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Serum IGF-1 and the Risk of Cardio-Kidney Outcomes in Metabolic Dysfunction-Associated Steatotic Liver Disease

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) increases cardiovascular and kidney disease risk. Insulin-like growth factor 1 (IGF-1) regulates metabolic and vascular function, but its role in long-term cardio-kidney outcomes (CKO) in MASLD remains unclear. This study examined the association between MASLD, IGF-1 levels and CKO.

Methods: In this prospective cohort study, we used data from 214 512 UK Biobank participants without baseline cardiovascular or chronic kidney disease (CKD). Participants were categorized into four groups: no-MASLD and MASLD stratified by age- and sex-specific tertiles of serum IGF-1 (T1–T3). The primary outcome was a composite CKO; secondary outcomes were incident CKD and 3-point major adverse cardiovascular events (3P-MACE).

Results: Over a median 13-year follow-up, 20 395 CKOs occurred. MASLD increased event rates across all IGF-1 tertiles ($p < 0.001$), with a significant interaction observed between MASLD and IGF-1 levels (P for interaction $= 0.014$). In multivariable Cox models, MASLD remained independently associated with CKO risk, strongest in the lowest IGF-1 tertile (T1: adjusted hazards ratio [aHR], 1.24 [95% CI: 1.18–1.30] vs. no-MASLD). Similar trends were observed for incident CKD (T1: aHR, 1.35 [95% CI: 1.22–1.49]) and 3P-MACE (T1: aHR, 1.26 [95% CI: 1.18–1.35]). Subgroup analyses indicated consistent associations across sex, BMI and diabetes, with stronger effects in participants < 65 years and markedly greater CKD risk among those with baseline albuminuria.

Conclusion: MASLD independently predicted CKO, particularly among individuals with low IGF-1 levels. Incorporating IGF-1 into clinical evaluations may improve risk stratification beyond conventional metabolic factors.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease, has emerged as a global public health concern, affecting a substantial proportion of adults worldwide [1, 2]. Beyond its hepatic manifestations, MASLD is increasingly being recognized as a multisystem disorder with profound extrahepatic consequences. Notably, cardiovascular disease (CVD), rather than liver-related complications, is the leading cause of morbidity and mortality in MASLD [3–6]. Furthermore,

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MASLD and chronic kidney disease (CKD) have a strong bidirectional relationship, with each accelerating the risk and progression of the other [7]. This interconnection underscores the concept of the cardio-kidney-metabolic (CKM) axis and highlights the need for biomarkers that can identify patients at high risk for adverse cardio-kidney outcomes [8–10].

Insulin-like Growth Factor 1 (IGF-1) is a pleiotropic hormone with a structure similar to insulin and is essential for cellular growth, metabolism and systemic homeostasis [11]. The liver is the primary site of circulating IGF-1 synthesis, which is tightly regulated by the growth hormone (GH) axis [12]. Hepatic injury and metabolic dysfunction, as in MASLD, characterized by steatosis, inflammation, and fibrosis, can impair IGF-1 production, and reduced levels of serum IGF-1 have been consistently associated with more severe disease [13]. In the general population, the significance of the GH/IGF-1 axis in maintaining CKM health is well established. Low IGF-1 levels have been associated with atherosclerosis, endothelial dysfunction, heart failure and major adverse cardiovascular events (MACE) [14, 15]. Although the evidence remains controversial, several studies have shown that IGF-1 deficiency is associated with reduced glomerular filtration [16, 17]. Nevertheless, the prognostic role of IGF-1 in MASLD remains unclear. Most previous studies were limited by small sample sizes, cross-sectional designs, or a narrow focus on either cardiovascular or kidney outcomes without simultaneous evaluation of both.

Therefore, this study aimed to investigate the association between serum IGF-1 levels and the risk of major adverse cardiovascular and kidney outcomes in individuals with or without MASLD using data from the UK Biobank, a large prospective population-based cohort.

2 | Methods

2.1 | Study Population and Data Source

A prospective cohort study was conducted using data from the UK Biobank, a large-scale population-based study that recruited over 500000 participants aged 40–69 years across the United Kingdom, between 2006 and 2010. A detailed description of the UK Biobank protocol has been previously published [18]. Comprehensive data on demographics, lifestyle factors and medical histories were collected at the baseline assessment visit. All the participants underwent physical measurements and provided biological samples for biochemical analyses. Follow-up data were available for this study from March 31, 2023.

The final analytical cohort was derived after applying several exclusion criteria (Figure 1). First, participants with a baseline history of cancer, other liver diseases (e.g., viral or autoimmune hepatitis), or prevalent CVD were excluded, in addition to individuals with pre-existing CKD, defined as an estimated glomerular filtration rate (eGFR) $< 60\,\mathrm{mL/min/1.73m^2}$ at baseline, and those with significant alcohol consumption (weekly intake > 210 g for men and > 140 g for women). After applying all exclusion criteria, 214512 participants with available baseline serum IGF-1 levels were included in the final analysis. This study was conducted under the UK Biobank application number 72527. UK Biobank received ethical approval from the Northwest Multicenter Research Ethics Committee. The Massachusetts General Hospital Institutional Review Board approved the secondary data analysis. All participants provided electronically signed informed consent. This study adhered to the Strengthening the Reporting of Observational Studies in

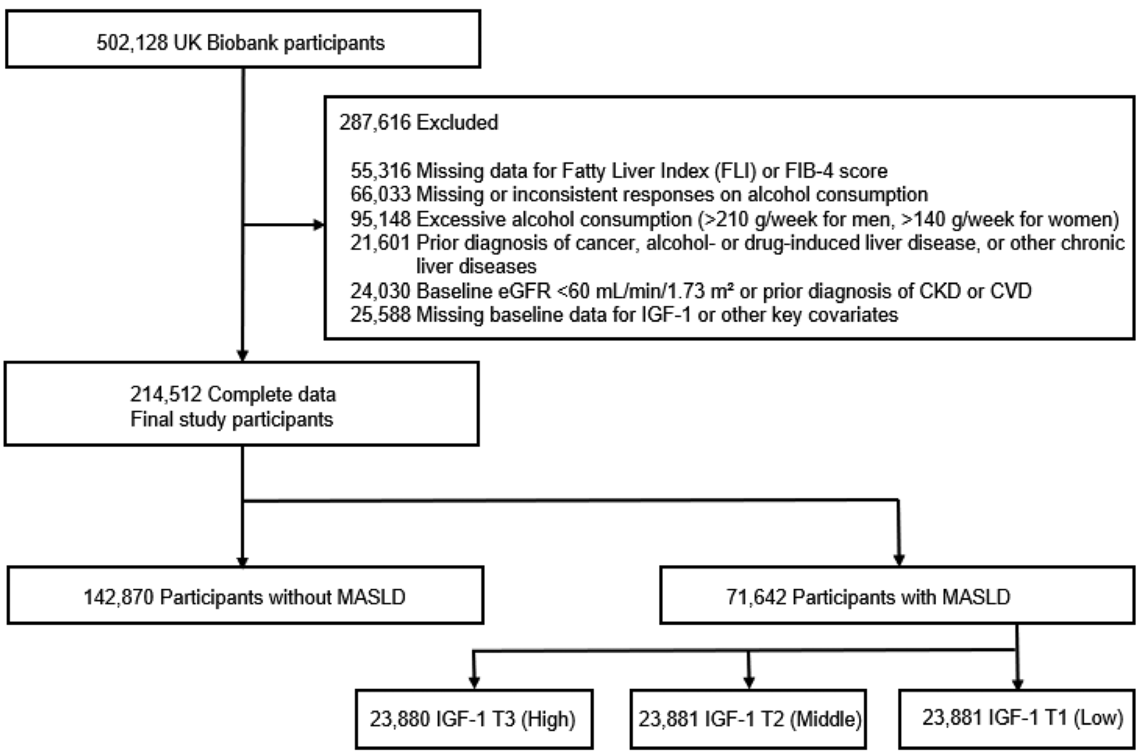

FIGURE 1 | Study subject. Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IGF-1, insulin-like growth factor 1; MASLD, metabolic dysfunction-associated steatotic liver disease.

Epidemiology (STROBE) guidelines and was conducted in accordance with the Declaration of Helsinki.

2.2 | Definition of MASLD and IGF-1 Stratification

MASLD was defined according to the recent consensus guidelines, requiring the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor. Hepatic steatosis was identified using the Fatty Liver Index (FLI) with a validated cutoff of 60. Cardiometabolic risk factors included overweight or obesity, hyperglycemia, hypertension and dyslipidemia (high triglycerides or low high-density lipoprotein cholesterol [HDL-C] levels). For primary analyses, participants were classified into four mutually exclusive groups. The reference group comprised individuals without MASLD. Participants with MASLD were stratified into three groups based on age- and sex-specific serum IGF-1 levels, which were derived exclusively from the MASLD cohort. To establish these cohort-specific tertiles, participants with MASLD were first grouped by sex and predefined age categories (< 50, 50–59, 60–69 and ≥ 70 years). Within each stratum, the serum IGF-1 levels were categorized into the following tertiles: T1 (lowest), T2 (middle) and T3 (highest). Additionally, to formally test for a statistical interaction between MASLD and serum IGF-1 levels on a population scale, a second set of IGF-1 tertiles was defined based on distribution across the entire study cohort. These population-level tertiles were also stratified by age and sex and used specifically for the interaction analysis presented in the Supporting Information.

2.3 | Cardio-Kidney Outcomes

The primary outcome was a composite cardio-kidney endpoint that included incident CKD and 3-point MACE (3P-MACE). The secondary outcomes were incident CKD and 3P-MACE, analysed as separate endpoints. Outcomes were ascertained through linkage to the national Hospital Episode Statistics and death registry data. Incident CKD was defined as the first occurrence of a relevant diagnostic code (International Classification of Diseases, 10th Revision: N18.x) or surgical procedure code (Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4) indicating kidney transplantation, dialysis, or vascular access to renal replacement therapy. 3P-MACE were defined as a composite of nonfatal myocardial infarction, nonfatal ischemic stroke and cardiovascular death. The follow-up time for each participant was calculated from the date of the baseline assessment until the first occurrence of an outcome, death, or the end of the follow-up period, whichever occurred first.

2.4 | Statistical Analysis

Baseline characteristics of the study population were presented according to the four primary analysis groups (no-MASLD and MASLD stratified by internal IGF-1 tertiles). Continuous variables were summarized as medians with interquartile ranges (IQRs), while categorical variables were presented as counts and percentages. Differences between groups were assessed using the Kruskal–Wallis test for continuous variables and Pearson's chi-squared test for categorical variables, with pairwise comparisons between tertiles performed as appropriate. The cumulative incidence of outcomes was visualized using Kaplan–Meier curves, and differences between groups were evaluated using the log-rank test. Multivariable Cox proportional hazards models were used to estimate the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the association between the exposure groups and outcomes, using the no-MASLD group as the reference. The final multivariable Cox model was adjusted for a comprehensive set of potential confounders, including age, sex, body mass index (BMI), smoking status, alcohol intake, systolic and diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C) level, baseline eGFR, glycated haemoglobin (HbA1c) level, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and ethnicity. To formally test for effect modification by IGF-1, a multiplicative interaction term between MASLD status (yes/no) and population-level IGF-1 tertiles was included in the fully adjusted Cox model. The significance of this interaction was assessed using a likelihood ratio test. Internal risk comparisons within the MASLD cohort, using the MASLD-T3 group as a reference, were also conducted. Subgroup analyses were performed according to age, sex, BMI and diabetes. The proportional hazard assumption for all models was verified using Schoenfeld residuals. To assess potential non-linear associations, restricted cubic spline analyses were performed for serum IGF-1 levels with cardio-kidney outcomes using Cox proportional hazards models.

Several sensitivity analyses were performed to assess the robustness of the findings. First, to further validate the definition of MASLD, alternative approaches were applied; hepatic steatosis was defined using MRI-based proton density fat fraction (PDFF) in a subset of participants with imaging data, and MASLD was redefined using the hepatic steatosis index (HSI), with analyses repeated accordingly. Second, multivariable Cox models were additionally adjusted for the fibrosis-4 (FIB-4) index to account for liver fibrosis severity. Third, socioeconomic status (Townsend Deprivation Index, TDI) and serum triglyceride levels were further included in the multivariable Cox model. Fourth, participants were categorized into six groups based on population-wide tertiles of IGF-1 and MASLD status, and Cox proportional hazards models were used to assess the association with CKO. Finally, missing data were addressed using multiple imputation with chained equations, and analyses were repeated to evaluate the impact of missing data on the results.

Statistical significance was defined as a two-sided p-value < 0.05. All statistical analyses were performed using the R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Baseline Characteristics

In total, 214 512 participants were included in the analysis, of whom 142 870 were classified as no-MASLD and 71 642 as having MASLD. Baseline serum IGF-1 levels were significantly lower in patients with MASLD than in those without MASLD. For the primary analyses, the MASLD group was stratified into age- and sex-specific tertiles of serum IGF-1 (T3 [highest], $n = 23880$; T2 [middle], $n = 23881$; T1 [lowest], $n = 23881$; Table S1). The baseline characteristics of the four groups are shown in Table 1. Compared with individuals without MASLD, those with MASLD were older and had a more adverse cardiometabolic profile, including higher BMI, waist circumference, systolic and diastolic blood pressures, fasting glucose, HbA1c and triglycerides levels, and lower HDL cholesterol.

Among the MASLD cohort, a clear metabolic gradient was observed across IGF-1 tertiles, with the most pronounced differences seen in the levels of HbA1c and C-reactive protein. Participants in the IGF-1 T1 group had the most unfavourable metabolic phenotype, characterized by the highest BMI, waist circumference and prevalence of type 2 diabetes and hypertension. The IGF-1 T1 group also had a greater proportion of current smokers and alcohol consumers and a lower proportion of non-white participants. Furthermore, laboratory measurements in the IGF-1 T1 group showed higher levels of glucose, HbA1c, triglycerides, LDL cholesterol and C-reactive protein, and lower eGFR compared with the higher IGF-1 tertiles.

3.2 | Association of MASLD and IGF-1 Levels With Primary Outcome

During a median follow-up of 13 years, 20 395 composite cardio-kidney events were recorded. Kaplan–Meier analysis revealed a significantly higher cumulative incidence of events in all three MASLD groups than in the no-MASLD group (log-rank $p < 0.001$) (Figure 2). To statistically justify the stratification of MASLD by IGF-1 levels, a formal interaction between MASLD status and population-level IGF-1 tertiles was first tested for. A significant interaction between MASLD and IGF-1 levels was observed (P for interaction = 0.014), supporting potential effect modification, although individual interaction terms were not consistently statistically significant (Table S2). In multivariable Cox models for CKO, after full adjustment for potential confounders, all MASLD groups remained at a significantly increased risk of CKO compared with the no-MASLD group (Table 2). A graded inverse association was observed across IGF-tertiles, with progressively higher risk at lower IGF-1 levels and the highest risk in the lowest tertile (T1: aHR, 1.24, 95% CI: 1.18–1.30), followed by the T2 group (aHR, 1.10, 95% CI: 1.04–1.15) and the T3 group (aHR, 1.12, 95% CI: 1.07–1.18). In a direct comparison within the MASLD cohort (with T3 as the reference), the T1 group had a significantly higher risk for the composite outcome (aHR, 1.10, 95% CI: 1.04–1.15, $p < 0.001$) (Table S3). Restricted cubic spline analysis demonstrated a non-linear, inverse association between serum IGF-1 levels and CKO, with a steeper increase in risk observed at lower IGF-1 levels (Figure S1). This pattern was consistent in analyses stratified by MASLD status.

3.3 | Association of MASLD and IGF-1 Levels With Secondary Outcomes

When the secondary outcomes were analysed separately, the association with incident CKD showed a similar pattern, with the magnitude of risk being particularly pronounced in the T1 group (aHR, 1.35, 95% CI: 1.22–1.49 vs. no-MASLD) (Table 2). A significant association was also observed for 3P-MACE. The risk for 3P-MACE was elevated across all MASLD groups, again with the highest risk evident in the T1 tertile (aHR, 1.26, 95% CI: 1.18–1.35 vs. no-MASLD). The internal risk comparisons within the MASLD cohort for these outcomes are shown in Table S3.

3.4 | Subgroup Analyses

The association between the MASLD–IGF-1 groups and CKO was generally consistent across the major clinical subgroups (Table 3). A significant interaction was observed for age (P for interaction < 0.001), with stronger associations noted among participants < 65 years. In this group, the risk was highest for MASLD with the lowest IGF-1 tertile (aHR, 1.27 [95% CI: 1.20–1.35]), whereas associations were attenuated but remained significant in those aged ≥ 65 years (aHR, 1.19 [95% CI: 1.10–1.29]). No significant interactions were observed between sex (P for interaction = 0.114), BMI category (P for interaction = 0.270), or diabetes status (P for interaction = 0.310). Elevated risks were consistently observed across all subgroups, with the lowest IGF-1 tertile (T1) showing the highest risk, regardless of sex, BMI or diabetes status.

To further examine the robustness of the association between IGF-1 levels and incident CKD, subgroup analyses stratified by baseline albuminuria status were performed (Table S4). The association between the MASLD score and incident CKD was substantially modified by baseline albuminuria. Among participants without baseline albuminuria, the association was attenuated, with only the T1 group maintaining a statistically significant risk (aHR, 1.28 [95% CI: 1.15–1.44]). In contrast, the risks were markedly increased in patients with preexisting albuminuria. In this high-risk subgroup, all MASLD tertiles showed robust associations with incident CKD and aHRs of 1.55 for T3, 1.35 for T2 and 1.49 for T1.

3.5 | Sensitivity Analyses

First, to validate the definition of MASLD, alternative definitions of hepatic steatosis were applied, and the results remained consistent with the primary findings. In a subset of participants with available MRI-PDFF data, baseline MASLD classification was associated with higher liver fat content, and a graded increase in PDFF was observed across decreasing IGF-1 tertiles within the MASLD group (Table S5). Similarly, when MASLD was redefined using the HSI, the associations between MASLD, IGF-1 levels and CKO remained robust, with the highest risk observed in the lowest IGF-1 tertile (Table S6). Second, additional adjustment for the FIB-4 index to account for liver fibrosis severity did not materially alter the associations (Table S7). Third, further adjustment for socioeconomic status (TDI) and serum triglyceride levels did not materially alter the associations, and the results remained consistent with the primary analysis (Table S7). Fourth, in analyses using population-wide IGF-1 tertiles, participants were stratified into six groups based on MASLD status and IGF-1 levels. The results demonstrated a consistent pattern, with progressively higher risk observed among individuals with MASLD and lower IGF-1 levels, supporting the primary findings (Table S8). Finally, the proportion

TABLE 1 | Baseline demographic and clinical characteristics of the study cohort, stratified by MASLD status and serum IGF-1 tertiles.

Characteristic	No-MASLD ($n = 142870$)	MASLD, IGF-1 T3 (High) ($n = 23880$)	MASLD, IGF-1 T2 (Middle) ($n = 23881$)	MASLD, IGF-1 T1 (Low) ($n = 23881$)	p
Anthropometrics					
Age, years	57 (49–63)	58 (51–63)[a]	57 (50–63)[a]	58 (51–63)[a,b,c]	< 0.001
Sex, male	45 987 (32%)	13 998 (59%)	14 555 (61%)	13 701 (57%)	< 0.001
BMI, kg/m^2	24.8 (22.9–26.7)	30.2 (28.1–32.7)[a]	30.5 (28.3–33.4)[a,b]	31.5 (28.9–34.9)[a,b,c]	< 0.001
Weight, kg	69 (62–76)	88 (81–97)[a]	89 (82–98)[a,b]	91 (82–101)[a,b,c]	< 0.001
Waist circumference, cm	82 (76–89)	100 (95–105)[a]	101 (95–107)[a,b]	102 (96–110)[a,b,c]	< 0.001
SBP, mmHg	132 (121–146)	140 (130–152)[a]	140 (130–152)[a]	141 (130–153)[a,b]	< 0.001
DBP, mmHg	80 (73–86)	85 (79–92)[a]	86 (79–92)[a,b]	86 (79–92)[a,b]	< 0.001
Smoking status					< 0.001
Never	90 759 (64%)	13 440 (56%)	12 960 (54%)	12 476 (52%)	
Previous	41 185 (29%)	8341 (35%)	8622 (36%)	8913 (37%)	
Current	10 926 (7.6%)	2099 (8.8%)	2299 (9.6%)	2492 (10%)	
Alcohol intake					< 0.001
Never	9093 (6.4%)	1505 (6.3%)	1618 (6.8%)	2223 (9.3%)	
Previous	6313 (4.4%)	1281 (5.4%)	1432 (6.0%)	1805 (7.6%)	
Current	127 464 (89%)	21 094 (88%)	20 831 (87%)	19 853 (83%)	
Ethnicity					< 0.001
White	133 901 (94%)	22 472 (94%)	22 203 (93%)	21 757 (91%)	
Others	8969 (6%)	1408 (6%)	1678 (7%)	2124 (9%)	
Comorbidity					
Diabetes mellitus	4683 (3.3%)	2313 (9.7%)	2431 (10%)	3930 (16%)	< 0.001
Hypertension	66 826 (47%)	16 775 (71%)	16 831 (71%)	17 728 (75%)	< 0.001
Use of ACEi/ARBs	6493 (4.5%)	2733 (11%)	2553 (11%)	3041 (13%)	< 0.001
Laboratory measurements					
eGFR (mL/min/1.73 m^2)	91 (78–100)	81 (71–94)[a]	81 (71–95)[a,b]	84 (73–96)[a,b,c]	< 0.001
Glucose (mmol/L)	4.88 (4.57–5.22)	4.98 (4.65–5.40)[a]	4.99 (4.65–5.41)[a]	5.05 (4.69–5.58)[a,b,c]	< 0.001
HbA1c (mmol/mol)	34.6 (32.3–37.0)	36.0 (33.4–39.0)[a]	36.1 (33.6–39.1)[a,b]	36.8 (34.1–40.4)[a,b,c]	< 0.001
Triglycerides (mmol/L)	1.21 (0.91–1.63)	2.13 (1.59–2.88)[a]	2.15 (1.59–2.93)[a]	2.13 (1.57–2.92)[a]	< 0.001
LDL-C (mmol/L)	3.49 (2.97–4.06)	3.71 (3.11–4.31)[a]	3.72 (3.11–4.32)[a]	3.62 (2.98–4.25)[a,b,c]	< 0.001
HDL-C (mmol/L)	1.52 (1.30–1.78)	1.22 (1.06–1.42)[a]	1.20 (1.05–1.40)[a,b]	1.19 (1.03–1.38)[a,b,c]	< 0.001
CRP (mg/L)	0.94 (0.49–1.88)	1.70 (0.93–3.15)[a]	2.10 (1.14–3.90)[a,b]	2.73 (1.45–5.31)[a,b,c]	< 0.001

Note: Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. Post hoc pairwise comparisons were performed with Bonferroni correction for multiple testing.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor 1; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; SBP, systolic blood pressure.

[a] $p < 0.05$, vs. No-MASLD, by post hoc analysis (Bonferroni).
[b] $p < 0.05$, vs. MASLD, IGF-1 T3, by post hoc analyses.
[c] $p < 0.05$, vs. MASLD, IGF-1 T2, by post hoc analyses.

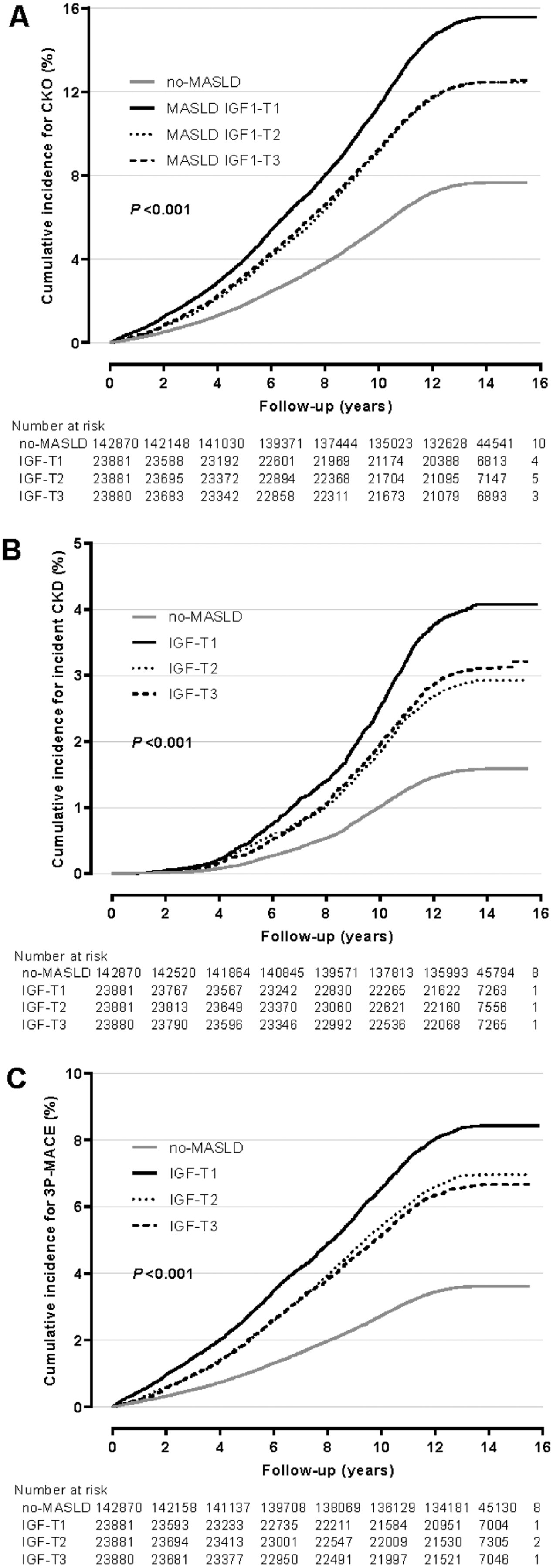

FIGURE 2 | Legend on next page.

FIGURE 2 | Kaplan–Meier curve for (A) CKO, (B) incident CKD and (C) 3P-MACE. Abbreviations: 3P-MACE, 3 point-major cardiovascular events; CKD, chronic kidney disease; CKO, cardio-kidney outcome; IGF-1, insulin-like growth factor 1; MASLD, metabolic dysfunction-associated steatotic liver disease.

TABLE 2 | Association between MASLD status stratified by IGF-1 tertiles and the risk of the composite cardio-kidney outcome.

				Model 1[b]		Model 2[c]		Model 3[d]	
Group	**Events**	**1000 PYs**	**Rate[a]**	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Cardiorenal outcome									
No-MASLD	10822	1877.5	5.76	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
MASLD with IGF-1 T3	2947	305.9	9.63	1.68 (1.61–1.75)	< 0.001	1.48 (1.42–1.54)	< 0.001	1.12 (1.07–1.18)	< 0.001
MASLD with IGF-1 T2	2948	306.8	9.61	1.67 (1.61–1.74)	< 0.001	1.47 (1.41–1.53)	< 0.001	1.10 (1.04–1.15)	< 0.001
MASLD with IGF-1 T1	3678	301.7	12.19	2.12 (2.05–2.21)	< 0.001	1.80 (1.74–1.87)	< 0.001	1.24 (1.18–1.30)	< 0.001
Incident CKD									
No-MASLD	2189	1901.7	1.15	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
MASLD with IGF-1 T3	712	313.4	2.27	1.98 (1.82–2.16)	< 0.001	2.13 (1.95–2.32)	< 0.001	1.18 (1.07–1.30)	0.001
MASLD with IGF-1 T2	669	314.6	2.13	1.86 (1.70–2.02)	< 0.001	2.01 (1.84–2.20)	< 0.001	1.13 (1.02–1.25)	0.025
MASLD with IGF-1 T1	923	311.3	2.96	2.59 (2.40–2.80)	< 0.001	2.63 (2.44–2.85)	< 0.001	1.35 (1.22–1.49)	< 0.001
3P-MACE									
No-MASLD	5068	1886.0	2.69	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
MASLD with IGF-1 T3	1548	308.4	5.02	1.87 (1.76–1.98)	< 0.001	1.51 (1.42–1.60)	< 0.001	1.16 (1.09–1.24)	< 0.001
MASLD with IGF-1 T2	1625	309.2	5.25	1.96 (1.85–2.07)	< 0.001	1.56 (1.48–1.65)	< 0.001	1.17 (1.09–1.25)	< 0.001
MASLD with IGF-1 T1	1959	304.9	6.42	2.39 (2.27–2.52)	< 0.001	1.87 (1.78–1.98)	< 0.001	1.26 (1.18–1.35)	< 0.001

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; IGF-1, insulin-like growth factor 1; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease.
[a]Incidence rate per 1000 person-years.
[b]Model 1: Crude model.
[c]Model 2: Adjusted for age and sex.
[d]Model 3: Adjusted for age, sex, BMI, smoking, alcohol intake, systolic and diastolic blood pressure, LDL cholesterol, baseline eGFR, HbA1c, use of ACE inhibitors/ARBs and ethnicity.

TABLE 3 | Subgroup analyses for the association between MASLD groups and the risk of the composite cardio-kidney outcome.

		No MASLD	MASLD, T3	MASLD, T2	MASLD, T1	
Subgroup	**Category**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	***P* for Interaction**
Age						< 0.001
	< 65 years	1.00 (Reference)	1.15 (1.08–1.22)	1.12 (1.05–1.19)	1.27 (1.20–1.35)	
	≥ 65 years	1.00 (Reference)	1.09 (1.00–1.18)	1.06 (0.98–1.16)	1.19 (1.10–1.29)	
Sex						0.114
	Men	1.00 (Reference)	1.12 (1.05–1.19)	1.10 (1.03–1.17)	1.17 (1.10–1.25)	
	Women	1.00 (Reference)	1.13 (1.05–1.22)	1.09 (1.01–1.18)	1.31 (1.22–1.42)	
BMI						0.270
	< 25 kg/m^2	1.00 (Reference)	1.35 (1.06–1.71)	1.20 (0.92–1.57)	1.43 (1.11–1.84)	
	≥ 25 kg/m^2	1.00 (Reference)	1.12 (1.06–1.18)	1.10 (1.04–1.15)	1.23 (1.17–1.29)	
Diabetes						0.310
	No	1.00 (Reference)	1.11 (1.05–1.17)	1.10 (1.04–1.16)	1.25 (1.19–1.32)	
	Yes	1.00 (Reference)	1.16 (1.02–1.31)	1.07 (0.94–1.21)	1.14 (1.01–1.29)	

Note: All models were adjusted for age, sex, BMI, smoking status, alcohol intake, systolic and diastolic blood pressure, LDL cholesterol, baseline eGFR, HbA1c, use of ACE inhibitors/ARBs and ethnicity, unless the variable was used for stratification.
Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; IGF-1, insulin-like growth factor 1; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease.

of missing data was low (0%–5.2% across covariates; Table S9). In sensitivity analyses using multiple imputation, the associations remained materially unchanged, supporting the robustness of the primary findings (Table S10).

4 | Discussion

In this large prospective cohort of 214 512 participants from the UK Biobank, MASLD was consistently associated with an increased risk of CKO compared with no-MASLD. Importantly, the prognostic impact of MASLD differed according to circulating IGF-1 levels, with progressively higher riskobserved at lower IGF-1 levels and the highest risk in the lowest tertile. Participants in the MASLD group with low IGF-1 levels had a 24% higher risk of composite CKO, and were also at a significantly increased risk of both incident CKD and 3P-MACE. Subgroup analyses showed that the associations were consistent across sex, BMI and diabetes, stronger in participants < 65 years of age and markedly amplified for incident CKD in those with baseline albuminuria among individuals with CKD.

IGF-1 plays a pivotal role in MASLD and affects the hepatic outcomes and diverse metabolic complications. In patients with type 2 diabetes, Miyauchi et al. reported that lower serum IGF-1 levels were inversely correlated with non-invasive markers of liver fibrosis, suggesting that IGF-1 deficiency reflects more advanced hepatic injury within metabolic liver disease populations [19]. Similarly, recent reviews of MASLD pathophysiology have highlighted the endocrine role of the liver, emphasizing that disruption of GH signalling and reduced IGF-1 synthesis are central to the progression from steatosis to inflammation and fibrosis [20, 21]. Consistent with this, a meta-analysis of patients with cirrhosis and advanced hepatitis found that low serum IGF-1 was a strong predictor of transplant-free survival [22]. Evidence from obesity studies further supports this hypothesis. In a prospective study of 79 individuals with severe obesity undergoing metabolic surgery, investigators observed marked improvements in GH, IGF-1 and insulin-like growth factor binding protein 1 (IGFBP1) levels over 52 weeks, accompanied by weight loss, enhanced insulin sensitivity and reductions in systemic inflammation [23]. Notably, the increase in IGF-1 was not correlated with changes in body weight or leptin, but rather with improvements in adipose tissue function and decreased high-sensitivity CRP, underscoring the role of inflammation in regulating the GH–IGF-1 axis. These findings reinforce the hepatic and metabolic determinants of IGF-1 and its potential utility as a biomarker of MASLD severity.

Beyond hepatic outcomes, large-scale epidemiological studies have demonstrated an association between IGF-1 and cardiovascular risk in the general population. In a meta-analysis of prospective cohorts, both low and high IGF-1 levels were associated with an increased risk of coronary artery disease, heart failure and stroke, with evidence of a nonlinear (U- or J-shaped) relationship [15]. However, evidence regarding kidney outcomes remains limited. In a cross-sectional analysis of 5388 adults from the third National Health and Nutrition Examination Survey conducted in the united states, higher serum IGF-1 concentrations were independently associated with prevalent CKD, with participants in the highest quartile showing more than a twofold higher odds than those in the lowest quartile [24]. Similarly, in a randomized controlled trial of 2627 individuals with type 2 diabetes and CKD, elevated IGF-1 levels were associated with a greater risk of composite kidney outcome, including doubling of serum creatinine, cardiorenal death and all-cause mortality [25]. This apparent discrepancy likely reflects differences in disease context and underlying biology [26]. In advanced CKD and diabetes, higher IGF-1 levels may reflect compensatory activation of the growth hormone–IGF-1 axis, altered IGF-binding protein dynamics, or reduced renal clearance, thereby functioning as a marker of disease severity rather than a protective factor [24, 25]. In contrast, in a relatively healthier, community-based MASLD population, lower IGF-1 levels are more likely to indicate impaired hepatic synthetic function, metabolic dysregulation and systemic inflammation [13]. We therefore hypothesize that IGF-1 may have a context-dependent role that higher levels reflect disease burden in advanced CKD, whereas lower levels identify individuals with compromised metabolic and hepatic health in MASLD. Consistent with this framework, we observed that lower IGF-1 levels were associated with more adverse metabolic and inflammatory profiles and higher cardio-kidney risk. Importantly, we observed a statistically significant interaction between MASLD and IGF-1 levels; however, this should be interpreted with caution given that individual interaction terms were not consistently significant. Nevertheless, the overall pattern suggests that IGF-1 may act as a modifier of MASLD-related cardio-kidney risk, with potential systemic implications extending beyond the liver to the cardiorenal axis.

Notably, the strong association between low IGF-1 levels and incident CKD in our MASLD cohort was a key finding. The link between MASLD and CKD is multifactorial, involving shared pathways of insulin resistance, systemic inflammation, oxidative stress and activation of the renin-angiotensin-aldosterone system [27]. IGF-1 itself plays a vital role in maintaining renal homeostasis by promoting glomerular filtration, renal blood flow and tubular function [28]. IGF-1 deficiency, as observed in our T1 group, may therefore exacerbate renal vulnerability in several ways. It can directly impair glomerular hemodynamics or contribute to renal fibrosis and endothelial dysfunction, compounding the profibrotic and inflammatory milieu already established by MASLD. Although formal mediation analyses were not performed, our findings provide indirect support for these pathways. Lower IGF-1 levels were associated with more adverse metabolic profiles and higher levels of inflammatory markers, including C-reactive protein, suggesting that both metabolic dysregulation and systemic inflammation may contribute to the observed associations. The marked amplification of the risk in participants with baseline albuminuria suggests that low IGF-1 levels may act as a 'second hit', accelerating the progression of kidney damage in individuals with preexisting renal vulnerability. Although the association was more pronounced for kidney outcomes, the link between low IGF-1 and 3P-MACE was also significant and clinically relevant. Cardiovascular disease is the leading cause of death in patients with MASLD, driven by atherogenic dyslipidemia, hypertension and a pro-inflammatory, pro-thrombotic state [3–5, 29–31]. Low IGF-1 levels have been independently linked to atherosclerosis, impaired cardiac function and endothelial dysfunction in the general population [32–35]. In the context of MASLD, low IGF-1 may indicate a more severe systemic metabolic derangement that promotes the development and progression of atherosclerosis. The risk observed in this study was primarily driven by the lowest IGF-1 tertile, consistent with a graded inverse association between IGF-1 levels and outcomes.

These findings have important clinical implications. Current risk stratification in MASLD focuses on metabolic comorbidities and hepatic fibrosis, but does not fully capture systemic risk. The incorporation of IGF-1, a simple and inexpensive biomarker, could improve risk prediction and guide early intervention. Clinically, low IGF-1 levels may help to identify individuals who would benefit from more intensive monitoring of blood pressure, glucose and kidney function. The consistency of the associations across sex, BMI and diabetes strata, as well as the amplification of risk in patients with albuminuria, suggests that IGF-1 provides incremental value beyond the established factors. Furthermore, these results raise the possibility that the GH/IGF-1 axis could represent a novel therapeutic target for reducing the systemic complications of MASLD.

This study had some limitations that must be acknowledged. First, MASLD was defined using the FLI, a non-invasive index, rather than imaging or histopathology, which may lead to misclassification. However, our findings were consistent across multiple sensitivity analyses using alternative definitions of hepatic steatosis. Second, serum IGF-1 levels were measured only at baseline, and changes could not be justified over time. Third, despite extensive adjustments, residual confounders from unmeasured variables could not be entirely excluded. Fourth, CKD outcomes were defined using diagnostic and procedure codes rather than repeated measurements of eGFR or proteinuria, due to limited availability of longitudinal laboratory data. This approach may have led to misclassification of CKD events. Finally, our cohort consisted predominantly of individuals of White European ancestry, which may have limited the generalizability of these findings to other ethnic groups.

In conclusion, this study provides strong evidence that MASLD is an independent risk factor for adverse cardio-kidney events. Low serum IGF-1 is a potent biomarker that stratifies individuals with MASLD, who are particularly vulnerable to developing future cardiovascular and kidney diseases. Future research should validate these findings in diverse populations and explore the therapeutic potential of targeting the GH/IGF-1 axis in patients with MASLD.

Author Contributions

Y.I.J., H.-S.P. and T.S.L. contributed to the research idea and study design; J.H.J. was responsible for data acquisition; Y.C. and J.H.J. contributed to data analysis/interpretation; H.-S.P., Y.I.J. and J.H.J. performed the statistical analyses; and J.H.J. was the guarantor. Each author contributed important intellectual content during manuscript drafting or revision, and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work were appropriately investigated and resolved.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70792.

References

1. G. Targher, L. Valenti, and C. D. Byrne, "Metabolic Dysfunction-Associated Steatotic Liver Disease," *New England Journal of Medicine* 393, no. 7 (2025): 683–698.

2. M. Israelsen, S. Francque, E. A. Tsochatzis, and A. Krag, "Steatotic Liver Disease," *Lancet* 404, no. 10464 (2024): 1761–1778.

3. M. Alexander, A. K. Loomis, J. van der Lei, et al., "Non-Alcoholic Fatty Liver Disease and Risk of Incident Acute Myocardial Infarction and Stroke: Findings From Matched Cohort Study of 18 Million European Adults," *BMJ* 367 (2019): l5367.

4. A. Mantovani, A. Csermely, G. Petracca, et al., "Non-Alcoholic Fatty Liver Disease and Risk of Fatal and Non-Fatal Cardiovascular Events: An Updated Systematic Review and Meta-Analysis," *Lancet Gastroenterology and Hepatology* 6, no. 11 (2021): 903–913.

5. A. Mantovani, G. Petracca, A. Csermely, et al., "Non-Alcoholic Fatty Liver Disease and Risk of New-Onset Heart Failure: An Updated Meta-Analysis of About 11 Million Individuals," *Gut* 72 (2023): 372–380.

6. H.-H. Lee, H. A. Lee, E.-J. Kim, et al., "Cardiovascular Risk From Metabolic Dysfunction-Associated Steatotic Liver Disease, Cardiometabolic Risk Factor Count, and Their Longitudinal Changes: A Nationwide Cohort Study," *Official Journal of the American College of Gastroenterology|ACG* 120, no. 10 (2025): 2321–2329.

7. A. Mantovani, G. Petracca, G. Beatrice, et al., "Non-Alcoholic Fatty Liver Disease and Risk of Incident Chronic Kidney Disease: An Updated Meta-Analysis," *Gut* 71, no. 1 (2022): 156–162.

8. C. E. Ndumele, J. Rangaswami, S. L. Chow, et al., "Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association," *Circulation* 148, no. 20 (2023): 1606–1635.

9. J. H. Jhee, K. H. Ha, D. Son, et al., "Cumulative Cardiovascular Health Score Through Young Adulthood and Cardiovascular and Kidney Outcomes in Midlife," *JAMA Cardiology* 10 (2025): 1207–1212.

10. H. H. Lee, J. H. Jhee, E. J. Kim, et al., "Association Between the Ideal Cardiovascular Health Score and Cardiovascular-Kidney Outcomes in Young Adults," *American Journal of Kidney Diseases* 86, no. 4 (2025): 499–509.

11. D. LeRoith and S. Yakar, "Mechanisms of Disease: Metabolic Effects of Growth Hormone and Insulin-Like Growth Factor 1," *Nature Clinical Practice Endocrinology and Metabolism* 3, no. 3 (2007): 302–310.

12. A. Adamek and A. Kasprzak, "Insulin-Like Growth Factor (IGF) System in Liver Diseases," *International Journal of Molecular Sciences* 19, no. 5 (2018): 1308.

13. R. D. Kineman, M. del Rio-Moreno, and D. J. Waxman, "Liver-Specific Actions of GH and IGF1 That Protect Against MASLD," *Nature Reviews Endocrinology* 21, no. 2 (2025): 105–117.

14. E. Conti, C. Carrozza, E. Capoluongo, et al., "Insulin-Like Growth Factor-1 as a Vascular Protective Factor," *Circulation* 110, no. 15 (2004): 2260–2265.

15. J. Lin, L. Yang, J. Huang, et al., "Insulin-Like Growth Factor 1 and Risk of Cardiovascular Disease: Results From the UK Biobank Cohort Study," *Journal of Clinical Endocrinology and Metabolism* 108, no. 9 (2023): e850–e860.

16. J. Frystyk, P. Ivarsen, C. Skjaerbaek, A. Flyvbjerg, E. B. Pedersen, and H. Orskov, "Serum-Free Insulin-Like Growth Factor I Correlates With Clearance in Patients With Chronic Renal Failure," *Kidney International* 56, no. 6 (1999): 2076–2084.

17. F. Perticone, R. Maio, A. Sciacqua, et al., "Insulin-Like Growth Factor-1 and Glomerular Filtration Rate in Hypertensive Patients," *Journal of Hypertension* 27, no. 3 (2009): 613–617.

18. C. Sudlow, J. Gallacher, N. Allen, et al., "UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age," *PLoS Medicine* 12, no. 3 (2015): e1001779.

19. S. Miyauchi, T. Miyake, M. Miyazaki, et al., "Insulin-Like Growth Factor-1 Is Inversely Associated With Liver Fibrotic Markers in Patients With Type 2 Diabetes Mellitus," *Journal of Diabetes Investigation* 10, no. 4 (2019): 1083–1091.

20. A. L. Hutchison, F. Tavaglione, S. Romeo, and M. Charlton, "Endocrine Aspects of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): Beyond Insulin Resistance," *Journal of Hepatology* 79, no. 6 (2023): 1524–1541.

21. K. Rufinatscha, C. Ress, S. Folie, et al., "Metabolic Effects of Reduced Growth Hormone Action in Fatty Liver Disease," *Hepatology International* 12, no. 5 (2018): 474–481.

22. Y. Liu, H. Xue, Y. Liu, et al., "Serum Insulin-Like Growth Factor 1 and the Prognosis of Patients With Advanced Liver Diseases: A Meta-Analysis," *Clinical and Translational Gastroenterology* 16, no. 7 (2025): e00829.

23. S. Gancheva, S. Kahl, C. Herder, et al., "Metabolic Surgery-Induced Changes of the Growth Hormone System Relate to Improved Adipose Tissue Function," *International Journal of Obesity* 47, no. 6 (2023): 505–511.

24. S. Teppala, A. Shankar, and C. Sabanayagam, "Association Between IGF-1 and Chronic Kidney Disease Among US Adults," *Clinical and Experimental Nephrology* 14, no. 5 (2010): 440–444.

25. R. Mohebi, Y. Liu, M. K. Hansen, et al., "Insulin Growth Factor Axis and Cardio-Renal Risk in Diabetic Kidney Disease: An Analysis From the CREDENCE Trial," *Cardiovascular Diabetology* 22, no. 1 (2023): 176.

26. P. Kamenický, G. Mazziotti, M. Lombès, A. Giustina, and P. Chanson, "Growth Hormone, Insulin-Like Growth Factor-1, and the Kidney: Pathophysiological and Clinical Implications," *Endocrine Reviews* 35, no. 2 (2014): 234–281.

27. L. A. Bach, "The Insulin-Like Growth Factor System in Kidney Disease and Hypertension," *Current Opinion in Nephrology and Hypertension* 21, no. 1 (2012): 86–91.

28. L. A. Bach and L. J. Hale, "Insulin-Like Growth Factors and Kidney Disease," *American Journal of Kidney Diseases* 65, no. 2 (2015): 327–336.

29. A. Mantovani, R. Morandin, E. Sani, et al., "MASLD Is Associated With an Increased Long-Term Risk of Atrial Fibrillation: An Updated Systematic Review and Meta-Analysis," *Liver International* 45, no. 1 (2025): e16128.

30. A. Juul, T. Scheike, M. Davidsen, J. Gyllenborg, and T. Jørgensen, "Low Serum Insulin-Like Growth Factor I Is Associated With Increased Risk of Ischemic Heart Disease: A Population-Based Case-Control Study," *Circulation* 106, no. 8 (2002): 939–944.

31. H. Saber, J. J. Himali, A. S. Beiser, et al., "Serum Insulin-Like Growth Factor 1 and the Risk of Ischemic Stroke: The Framingham Study," *Stroke* 48, no. 7 (2017): 1760–1765.

32. X. Xu, M. Yi, C. Xiao, et al., "IGF-1 Provides Protective Role in Arteriosclerotic Cerebral Small Vessel Disease," *Hypertension* 82, no. 6 (2025): 1137–1150.

33. A. Bayes-Genis, C. A. Conover, and R. S. Schwartz, "The Insulin-Like Growth Factor Axis: A Review of Atherosclerosis and Restenosis," *Circulation Research* 86, no. 2 (2000): 125–130.

34. J. H. von der Thüsen, K. S. Borensztajn, S. Moimas, et al., “IGF-1 Has Plaque-Stabilizing Effects in Atherosclerosis by Altering Vascular Smooth Muscle Cell Phenotype,” *American Journal of Pathology* 178, no. 2 (2011): 924–934.

35. S. Ock, W. Ham, C. W. Kang, H. Kang, W. S. Lee, and J. Kim, “IGF-1 Protects Against Angiotensin II-Induced Cardiac Fibrosis by Targeting αSMA,” *Cell Death and Disease* 12, no. 7 (2021): 688.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Age- and Sex-Specific Thresholds for Serum IGF-1 Tertiles. **Table S2:** Cox proportional hazards model analysing the statistical interaction between MASLD status and population-level IGF-1 tertiles on the risk of the cardio-kidney outcome. **Table S3:** Internal comparison of the risk for the cardio-kidney outcomes across IGF-1 tertiles among participants within the MASLD cohort. **Table S4:** Association between MASLD groups and incident CKD with or without baseline albuminuria. **Table S5:** Validation of Baseline MASLD Classification with Follow-up MRI-PDFF ($n = 21\,174$). **Table S6:** Association between MASLD status defined by the hepatic steatosis index, stratified by IGF-1 tertiles, and the risk of the composite cardio-kidney outcomes. **Table S7:** Association between MASLD status stratified by IGF-1 tertiles and the risk of the composite cardio-kidney outcomes after additional adjustment for liver fibrosis severity, socioeconomic status and triglyceride levels. **Table S8:** Association between population-wide tertiles of IGF-1 combined with MASLD status and the risk of the composite cardio-kidney outcomes. **Table S9:** Missing data rates and baseline characteristics of covariates before multiple imputation. **Table S10:** Association between MASLD status stratified by IGF-1 tertiles and the risk of the composite cardio-kidney outcomes (Multiple Imputation Analysis). **Figure S1:** Restricted cubic spline analysis of the association between serum IGF-1 levels and the risk of cardio-kidney outcomes. (A) Overall population, (B) participants without MASLD and (C) participants with MASLD. Solid lines represent hazard ratios, and shaded areas indicate 95% confidence intervals.