Nonalcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals

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ABSTRACT

Objective: Recent studies reported an association between nonalcoholic fatty liver disease (NAFLD) and increased risk of new-onset heart failure (HF). However, the magnitude of the risk and whether this risk changes with severity of liver disease remains uncertain. We performed a meta-analysis of observational studies to quantify the magnitude of the association between NAFLD and risk of new-onset HF.

Design: We systematically searched Scopus, Web of Science and PubMed from database inception to March 2022 to identify eligible observational studies, in which NAFLD was diagnosed by serum biomarkers/scores, International Classification of Diseases (ICD) codes, imaging techniques or histology. The primary outcome was new-onset HF, as assessed mainly by ICD codes. Data from selected studies were extracted, and meta-analysis performed using random-effects models to obtain summary hazard ratios (HRs) with 95% CIs.

Results: We identified 11 longitudinal cohort studies with aggregate data on 11,242,231 middle-aged individuals from different countries and 97,716 cases of incident HF over a median of 10 years. NAFLD was associated with a moderately higher risk of new-onset HF (pooled random-effects 1.50, 95% CI 1.34-1.67, $p<0.0001$; $I^2=94.8\%$). This risk was independent of age, sex, adiposity measures, diabetes, hypertension and other common cardiovascular risk factors. Sensitivity analyses did not change these results. Funnel plot did not show any significant publication bias.

Conclusion: NAFLD is associated with a 1.5-fold higher long-term risk of new-onset HF, regardless of the presence of diabetes, hypertension and other common cardiovascular risk factors. However, the observational design of the studies does not allow for proving causality.

Key words: NAFLD; fatty liver; diabetes; heart failure; meta-analysis

SUMMARY BOX

What is already known about this topic: Recent observational studies have reported an association between nonalcoholic fatty liver disease (NAFLD) and higher risk of new-onset heart failure (HF). However, the magnitude of the risk and whether this risk changes with severity of liver disease remains uncertain.

What this study adds:

- This updated meta-analysis involving over 11 million middle-aged individuals from different countries shows that the risk of developing incident HF is 1.5-fold higher in individuals with NAFLD during a median follow-up of 10 years.
- The risk of incident HF is independent of age, sex, adiposity measures, diabetes, hypertension and other common cardiovascular risk factors.
- This risk also appears to increase further with greater severity of NAFLD, especially with higher fibrosis stage.

How this study might affect research, practice or policy: Health care professionals should be aware that risk of new-onset HF is moderately higher in patients with NAFLD. Because of the link between the two conditions, more careful surveillance of these patients will be needed.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become one of the most common causes of chronic liver diseases worldwide (affecting up to ~30% of the world's adults), and its global prevalence is expected to rise sharply over the next decade [1, 2, 3]. The clinical burden of NAFLD is not only restricted to its liver-related complications (nonalcoholic steatohepatitis [NASH], cirrhosis or hepatocellular carcinoma). Strong evidence now indicates that NAFLD is part of a multisystem disease that adversely affects several extra-hepatic organs, including the heart and vasculature [4, 5]. In fact, NAFLD not only promotes accelerated coronary atherosclerosis but also confers an increased risk of myocardial abnormalities (cardiac remodelling and hypertrophy) and certain arrhythmias (mostly permanent atrial fibrillation), which may precede and/or promote the development of new-onset heart failure (HF) [6, 7]. HF is increasingly becoming a major public and economic health burden worldwide. Its global prevalence is increasing due to the aging of the population, and HF is strongly associated with a higher risk of hospitalizations and all-cause mortality [8].

To our knowledge, there are only two meta-analyses that have recently assessed the association between NAFLD and the risk of developing incident HF [9, 10]. These two meta-analyses showed that NAFLD is significantly associated with a greater risk of incident HF. However, these two meta-analyses included a relatively small number of studies (with a maximum of 5 longitudinal studies) with a relatively modest sample size [9, 10]. In addition, these meta-analyses did not address the question of whether the strength of any association between NAFLD and risk of new-onset HF was affected by severity of NAFLD. Notably, as will be discussed below, in recent months a number of new cohort studies have examined the association between NAFLD and the risk of new-onset HF.

We have therefore undertaken an updated systematic review and meta-analysis of observational cohort studies to quantify the long-term risk of new-onset HF in individuals with NAFLD. We also aimed to explore whether the severity of NAFLD was associated with an increased risk of new-onset HF; and test the effect of recognised cardiometabolic risk factors as moderator variables on the association between NAFLD and risk of new-onset HF.

METHODS

Search strategy and selection criteria

We systematically searched three large electronic databases (Scopus, Web of Science and PubMed) from database inception to March 21, 2022, using pre-defined key words, to identify observational cohort studies examining the risk of new-onset HF events amongst adult (age ≥18 years) individuals with and without NAFLD. Search free text terms were "non-alcoholic fatty liver disease" ("NAFLD" OR "fatty liver" OR "non-alcoholic steatohepatitis" OR "NASH") AND risk of "incident heart failure" OR "heart failure". Searches were restricted to human studies. Studies in languages other than English were also excluded. We also reviewed references from original papers and review articles to identify further eligible studies not covered by our original database searches. This systematic review was performed according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [11]. Because the included studies were observational in design, we followed the reporting proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) for the meta-analysis of these studies [12].

Studies were included in the meta-analysis if they met the following criteria: 1) observational cohort studies assessing the association between NAFLD and risk of new-onset HF; 2) studies reporting hazard ratios (HRs) with 95% confidence intervals (95% CIs) for the outcome of interest; and 3) studies diagnosing NAFLD with serum liver enzyme levels, serum biomarkers/scores (e.g., fatty liver index [FLI] or other algorithmically-derived scores to diagnose the presence of hepatic steatosis), International Classification of Diseases (ICD) codes, imaging techniques or liver histology, in keeping with the diagnostic criteria for NAFLD. Participants included in the meta-analysis were both adult men and women without any restriction in terms of race or ethnicity.

Criteria for exclusion of the studies from the meta-analysis were as follows: 1) congress abstracts, case reports, reviews, practice guidelines, and case-control or cross-sectional studies; 2) cohort studies which did not specifically report any HR and 95% CIs for the outcome of interest; 3) cohort studies that included only patients with NAFLD or NASH

without a non-steatotic control group; and 4) cohort studies conducted in patients with type 2 diabetes, patients with established chronic or acute HF, or patients with established or suspected coronary artery disease.

Data extraction and quality assessment

Data from studies eligible for the aggregate data meta-analysis were extracted by three authors independently (AM, AC and GT). Disagreements at this level were resolved by consensus and a fourth author if needed (GP). For all studies, we extracted data on first author, publication year, study design, study country, population characteristics, methods used for NAFLD diagnosis, duration of follow-up, outcomes of interest, matching and confounding factors included in multivariable regression analyses. In case of multiple publications, we included the most up-to-date or comprehensive information.

Each eligible study was assessed for quality by using the Newcastle-Ottawa scale (NOS) by two independent reviewers (AM and GT), with disagreements resolved through consensus. The NOS uses a star system to evaluate a study in three domains: selection of participants (assigning a maximum of four stars), comparability of study groups (assigning a maximum of two stars), and ascertainment of outcomes of interest (assigning a maximum of three stars). Therefore, nine stars reflect the highest quality. We judged studies that received a score of 8 or 9 stars to be at low risk of bias, studies that scored 7 stars to be at medium risk, and those that scored ≤6 stars to be at high risk of bias. We recorded the reviewing authors' judgments, regarding the three NOS domains, in the risk of bias tool in the Review Manager software of the Cochrane collaboration [13].

Data synthesis and analysis

The primary outcome of interest of the meta-analysis was the risk of developing new-onset HF among individuals with NAFLD compared to NAFLD-free controls. In eligible studies the ascertainment of incident HF outcomes was based mainly on ICD-9 or ICD-10 codes or ascertained by revision of medical records. The HRs and 95% CIs were considered as the effect

size for each eligible study. In the case of studies reporting several HRs with varying degrees of covariate adjustment, HRs that reflected the maximum extent of adjustment for potential confounding factors, were extracted. The adjusted HRs of all eligible studies were then pooled, and an overall estimate of the effect-size was calculated using a random-effects model, as this methodology considers any differences between studies, even if there is no statistically significant heterogeneity [13].

Visual inspection of the forest plot was used to assess statistical heterogeneity. This was also assessed with the I^2-statistics, which provides an estimate of the percentage of variability across eligible studies that is due to heterogeneity rather than chance alone. Heterogeneity was considered to be low if I^2 is <25%, moderate if I^2 is between 25% and 75%, and high if I^2 is >75% [14]. The risk of publication bias was examined using the funnel plot and the Egger's regression test [13].

To explore the possible sources of heterogeneity across the studies and to test the robustness of the observed associations, we performed subgroup analyses by study country, length of follow-up, modality of HF diagnosis, modality of NAFLD diagnosis, and even after excluding studies using serum gamma-glutamyl-transferase (GGT) levels for diagnosing NAFLD. Univariable meta-regression analyses were also performed to test the effect of specific moderator variables (i.e., age, sex, ethnicity, body mass index, plasma total cholesterol levels, and percentage of hypertension, diabetes or prior acute myocardial infarction at baseline) on the effect size for the incidence of NAFLD-related HF events. Finally, we tested for possible excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies one at a time. All statistical tests were 2-sided, and p-value of <0.05 (two-tailed) was considered statistically significant. For analyses we used STATA® 16.1 (StataCorp, College Station, Texas, USA) and its meta-analysis package and R software (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria) with "*meta*" and "*metafor*" packages. The protocol of this systematic review was registered in advance on Open Science Framework, number osf.io/yu8zq.

Ethical Approval and Funding source

Ethical approval is not requested for a meta-analysis. There was no funding source for this study.

RESULTS

Characteristics of eligible studies

Figure 1 shows the results of the literature research and study selection. Based on the titles and abstracts of 490 selected citations (after excluding duplicates), we initially identified 17 potentially eligible studies from PubMed, Scopus or Web of Science databases prior to March 21, 2022 [15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31]. In **supplementary Table 1** the syntax used, and the records identified through database searches is presented. After examining the full text of these 17 potentially eligible studies, we excluded 6 studies, mainly due to unsatisfactory inclusion criteria or unsatisfactory outcome measures (as specified in **supplementary Table 2**) [26, 27, 28, 29, 30, 31]. As a result of these exclusions, we identified 11 unique, observational cohort studies for inclusion in the meta-analysis.

The main characteristics of the 11 eligible cohort studies are summarized in **Table 1**. Overall, these studies had aggregate data on 11,242,231 middle-aged individuals (50.1% women; mean age 55 years; mean BMI 26.4 kg/m^2). There were a total of 2,944,058 (26.2%) individuals with NAFLD at baseline and 97,716 incident cases of ICD-diagnosed HF over a median follow-up of 10.0 years (interquartile range: 8-14 years). Most of these studies recruited participants either from general populations or large health examination check-up programs, in which NAFLD was diagnosed by serum GGT levels, serum biomarkers/scores (FLI score), ICD codes, imaging techniques or liver histology. Four studies were carried out in Europe (Sweden, Finland, and UK), four studies were carried out in the United States and three studies were carried out in South Korea. Three studies used serum GGT levels for the diagnosis of NAFLD, four studies used the FLI score, two studies used ICD codes, one study used computed tomography, and one study used liver biopsy. The assessment of incident HF events on follow-up was based on ICD-9 or ICD-10 codes (n=7 studies), Hospital International

Classification of Diseases Adapted (HICDA) codes (n=1 study), or ascertained by revision of primary care records and/or hospitalization records (n=3 studies).

As reported in **supplementary Figure 1**, two studies received at least 8 stars on the NOS (i.e., studies at relatively low risk of bias), six studies received 7 stars (studies at medium risk of bias) and three studies received 6 stars (studies at high risk of bias), thus indicating an overall medium-low risk of bias.

NAFLD and risk of new-onset HF

The distribution of eligible studies by estimate of the association between NAFLD and the risk of developing new-onset HF is plotted in **Figure 2**.

The presence of NAFLD was associated with a moderately increased risk of incident HF (n=11 studies; pooled random-effects 1.50, 95% CI 1.34-1.67, p<0.0001; I^2=94.8%). Notably, since we have always used the fully adjusted HR estimates for each eligible study (as specified in **Table 1**), this pooled random-effects HR was independent of age, sex, adiposity measures, diabetes and other common cardiovascular risk factors. As also shown in **Figure 2**, the association between NAFLD and risk of new-onset HF was consistent even when the comparison was stratified by modality of NAFLD diagnosis (also reported in **Table 2**), except for the single cohort study that used computed tomography for diagnosing NAFLD in 719 older subjects. Additionally, in this study the diagnosis of NAFLD was based on cardiac computed tomography that examined only a single hepatic lobe (therefore being less accurate for complete structural assessment of the liver).

Subgroup analyses and meta-regressions

To explore the possible sources of heterogeneity across the eligible studies, we undertook subgroup analyses (**Table 2**). Notably, the association between NAFLD and risk of new-onset HF was consistent in all subgroups examined. In particular, the pooled random-effects HRs were essentially comparable after stratification by study country, follow-up length, modality

of HF diagnosis or after excluding the three cohort studies using serum GGT levels for diagnosing NAFLD.

As shown in **supplementary Figure 2,** the results of univariable meta-regression analyses to examine the effect of potential moderator variables showed a significant inverse association between age (p=0.020) or the proportion of those with pre-existing type 2 diabetes (p=0.022) and the risk of NAFLD-related HF events. Conversely, meta-regression analyses did not reveal any significant effect of sex, ethnicity, body mass index, plasma total cholesterol level or percentage of hypertension or prior acute myocardial infarction at baseline on the association between NAFLD and risk of new-onset HF.

We also tested for the possibility of excessive influence of individual cohort studies using an influence test that eliminated each of the included studies one at a time. Notably, eliminating each of the studies in turn from our pooled primary analysis did not reveal any significant influence on the overall risk of new-onset HF (**supplementary Figure 3**)**.**

Supplementary Figure 4 shows that there was no significant asymmetry of the funnel plot, thus suggesting that publication bias was unlikely (p=0.527 by the Egger's regression test).

NAFLD severity and risk of new-onset HF

The risk for incident HF appeared to further increase with more advanced liver disease, especially with higher levels of liver fibrosis, as assessed by non-invasive fibrosis biomarkers or histology (n=2 studies; pooled random-effects 1.76, 95% CI 0.75-4.36; I^2=96.9%). However, we believe that the results for the association between the severity of NAFLD and incident HF can only be discussed as a systematic review, due to insufficient data suitable for combining the studies in a meta-analysis. As shown in **Table 1**, there are only two cohort studies (from South Korea and Sweden) that examined the association between NAFLD severity and risk of new-onset HF. The study by Park *et al*. [23] in Korea reported that among participants with NAFLD, advanced liver fibrosis (as non-invasively assessed by BARD score ≥2) was associated

with a higher risk for new-onset HF (adjusted-HR 1.12, 95%CI 1.04-1.20). The study by Simon *et al.* [25] in Sweden reported that rates of incident HF increased progressively with the severity of NAFLD histology, with the highest incidence rates observed with non-cirrhotic fibrosis (adjusted-HR 2.04, 95%CI 1.66-2.51) and cirrhosis (adjusted-HR 2.83, 95%CI 2.08-3.85), after adjusting for age, sex and common cardiometabolic risk factors.

DISCUSSION

In this updated meta-analysis of 11 observational cohort studies (involving a total of about 11 million middle-aged individuals from different countries with ~98,000 cases of new-onset HF events over a median follow-up of 10 years), we found that NAFLD was significantly associated with a 1.5-fold higher risk of new-onset HF events (pooled random-effects 1.50, 95% CI 1.34-1.67, p<0.0001). Importantly, this risk was independent of age, sex, ethnicity, adiposity measures, pre-existing diabetes, hypertension and other common cardiovascular risk factors. Sensitivity analyses did not modify these results. In particular, the magnitude of this risk remained essentially unchanged even when the comparison was stratified by study country, follow-up duration, modality of HF diagnosis and modality of NAFLD diagnosis, or when we excluded from the analysis the three cohort studies using serum GGT levels for the diagnosis of NAFLD. Our meta-regression analyses also reported a significant inverse association between the proportion of patients with pre-existing diabetes at baseline and the risk of developing NAFLD-related HF events. This finding could be due, at least in part, to the fact that the coexistence of type 2 diabetes at baseline, which is a strong risk factor for HF [32], could attenuate the effect of NAFLD *itself* as a risk factor for new-onset HF, or alternatively, subjects with diabetes are often treated with a range of cardiovascular risk-reduction medications that could attenuate the risk of CVD and subsequent development of HF in this patient group. A similar hypothesis can also be proposed to explain the observed inverse association for age (older age, which is a strong risk factor for HF, could attenuate the effect of NAFLD *itself* as a risk factor for new-onset HF) and older people are more likely to be treated with medications that may attenuate risk of CVD and development of HF. It should also be noted that since NAFLD is also associated with a greater risk of developing incident diabetes [33], it is possible that during follow-up a larger number of patients will develop diabetes. Accordingly, the risk of new-onset HF should not be simply tested in

relation to the presence of diabetes at entry, but also as an effect of incident diabetes. Unfortunately, almost all of the eligible studies (except for one study [17]) did not have any data on occurrence of type 2 diabetes during the follow-up period (defined as a time-varying covariate). Finally, in this meta-analysis, we found that the risk of incident HF appeared also to increase further with greater severity of NAFLD, especially with higher fibrosis stage (as reported in the two cohort studies using liver biopsy or non-invasive scores of advanced fibrosis) [23, 25]. These latter observations are consistent with those of previous meta-analyses reporting a significant association between the presence and severity of NAFLD and the risk of developing adverse cardiovascular outcomes [34], atrial fibrillation [35], chronic kidney disease [36], or other extra-hepatic complications [33, 37]. These latter observations are also indirectly supported by longitudinal studies showing that increased fibrosis-4 (FIB-4) index or other non-invasive liver fibrosis risk scores are significantly associated with a higher risk of HF hospitalization and adverse cardiovascular outcomes in cohorts of patients with established NAFLD/NASH [31]. Similarly, these results are supported by data from cohorts of patients with established HF, especially in those with preserved ejection fraction (HFpEF) [38, 39]. However, this question remains to be fully resolved, and further studies are required to prove whether the severity of liver disease in NAFLD further amplifies the increased risk of developing incident HF.

To our knowledge, our meta-analysis assessing the association between NAFLD and the long-term risk of new-onset HF is the largest and most comprehensive assessment of this association to date. The results of our meta-analysis extend the observations of two recent smaller meta-analyses [9, 10]. In the first meta-analysis including 4 longitudinal studies (published until March 2021), Alon *et al.* [9] reported that NAFLD (as detected by either FLI score, ICD codes or computed tomography) was associated with a ~60% increased risk of new-onset HF (pooled random-effects HR 1.62, 95%CI 1.43-1.84; I^2=97%). However, no studies using liver biopsy for diagnosing NAFLD were included in this meta-analysis. In addition, among the four eligible studies included in the meta-analysis, the authors also included a cohort study by VanWagner *et al*. [28] who examined the longitudinal association of NAFLD with subclinical changes in myocardial structure and function, but not with new-onset HF. In the second meta-analysis that incorporated 5 longitudinal studies involving

about 1.4 million subjects (published until December 12, 2021), Salah *et al.* [10] reported that NAFLD was associated with a higher risk of new-onset HF (pooled random-effects HR 1.60, 95%CI 1.24-2.05; I^2=97%). Four of these 5 cohort studies have been also included in our meta-analysis; we excluded a small cohort study by Vita *et al*. [27] that included only patients who were suspected of having coronary artery disease. In contrast to our meta-analysis, in this meta-analysis the authors pooled the unadjusted HRs for each eligible study, so we cannot exclude that the association they observed between NAFLD and risk of new-onset HF, could be partly dependent on coexisting cardiometabolic risk factors. That said, in the two aforementioned meta-analyses the number of eligible studies was too small for performing subgroup analyses and meta-regressions, or for formally testing the existence of any significant publication bias. Compared to data from these two smaller meta-analyses [9, 10], we have more than doubled the total number of eligible studies (by including a total of 11 large cohort studies published until March 21, 2022); and we have also increased the sample size about 8-9 times (by including about 11.2 million people from different countries with aggregate data on ~98,000 cases of new-onset HF). In addition, we have also been able to test the effect of various established risk factors for HF as potential moderator variables, in the association between NAFLD and risk of new-onset HF.

It is beyond the scope of this meta-analysis to discuss the putative underlying mechanisms involved in the development of NAFLD-related HF and these have been discussed in a recent review of the subject [40]. There are probably several pathophysiological mechanisms by which NAFLD increases the risk of cardiac (functional, structural, and arrhythmic) complications that may promote the development of HF; NAFLD (especially advanced NAFLD with increasing levels of liver fibrosis) exacerbates systemic insulin resistance, promotes atherogenic dyslipidemia and releases multiple thrombogenic molecules, pro-inflammatory factors and oxidative stress biomarkers [6, 40]. In addition, there is growing scientific interest in the link between these two conditions because newer anti-hyperglycemic agents (such as sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists) exerting some benefit on hepatic fat content and histological resolution of NASH [41], have also documented clinically meaningful benefits on cardiovascular outcomes, including risk for HF hospitalization, regardless of the diabetes status [40, 42]. That said,

further research is needed to better decipher the complex pathophysiological mechanisms by which NAFLD may contribute to increase risk of new-onset HF.

The present meta-analysis has some important limitations, which are strictly inherent to the design of the eligible studies. First, the observational design of the eligible studies precludes us from assessing causality. Second, although most of these studies adjusted the results for age, sex and common cardiometabolic risk factors, the possibility of unmeasured and residual confounding cannot be ruled out. In particular, the large majority of these studies did not have any echocardiographic data for examining the association between NAFLD and different categories of left ventricular ejection fraction. As specified in **Table 1**, the only eligible study [22] that examined this association, showed that NAFLD was associated with a higher risk of developing HF with preserved ejection fraction (HFpEF) (adjusted-HR 1.24, 95%CI 1.14-1.34) versus HF with a reduced ejection fraction (HFrEF) (adjusted-HR 1.09, 95%CI 0.98-1.20). Third, most of the eligible studies have adjusted the results for pre-existing diabetes or plasma glucose concentrations at entry, but they did not adjust also for the effect of change in glucose tolerance status on the risk of new-onset HF during the follow-up period. Fourth, although we used a random-effects model, the interpretation of some results in this meta-analysis (like previously published meta-analyses [9, 10]) should be made cautiously, given the significant heterogeneity observed in the pooled primary analysis. We explored possible sources of heterogeneity using subgroup analyses and meta-regressions. It is reasonable to hypothesize that the significant heterogeneity likely reflects differences in the characteristics of study populations, study country, modality of NAFLD diagnosis, and severity of NAFLD. However, future individual participant data meta-analyses will provide a more detailed analysis of the possible sources of heterogeneity. Finally, we also included three cohort studies that used serum GGT levels as a proxy for diagnosing NAFLD. That said, our subgroup analyses showed that the exclusion of these three cohort studies from the analysis did not substantially change the significant association between NAFLD and risk of new-onset HF (**Table 2**).

Our study also has important strengths. Our meta-analysis includes data from large cohort studies from Asia, Europe and United States and the included subjects are likely to be an

accurate reflection of individuals worldwide with NAFLD, who are seen in routine clinical practice. The large number of incident cases of new-onset HF at follow-up also provides sufficiently high statistical power to quantify the magnitude of the association between NAFLD and the risk of new-onset HF. In addition, the overall quality of studies included in the meta-analysis was acceptable, according to the NOS scale. Finally, we did not extensively search for "grey literature", so a possible selective reporting bias of studies cannot be definitely excluded. However, we believe that our comprehensive search has made it unlikely that any published studies were missed. Moreover, visual inspection of the funnel plot and the Egger's regression test did not show any significant publication bias.

In conclusion, the results of this large and updated meta-analysis provide evidence that NAFLD is moderately associated with a higher risk of new-onset HF over a median follow-up of 10 years. Importantly, the increase in risk of new-onset HF with NAFLD is independent of age, sex, ethnicity, adiposity measures, diabetes, hypertension and other coexisting cardiovascular risk factors. Our data also suggest that the magnitude of this increase in risk seems to parallel the severity of NAFLD, especially the severity of liver fibrosis. We believe that the results of our meta-analysis further highlight the need for a patient-centred, multidisciplinary and holistic approach to manage both liver disease and cardiovascular risk in people with NAFLD[5]. Future high-quality prospective and mechanistic studies are certainly needed to better elucidate the existing but complex link between NAFLD and risk of new-onset HF; to examine whether genetic polymorphisms that increase risk of NAFLD (for example, the patatin-like phosholipase domain-containing 3 [*PNPLA3*] gene variant I148M and the trans-membrane 6 superfamily member 2 [*TM6SF2*] E167K variant) can modify risk of HF; and to test whether resolution or improvement of NAFLD (achieved by the use of newer anti-hyperglycemic drugs, such as glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors) may reduce risk of new-onset HF.

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Contributors: AM and GT designed the study. AM, GP, AC and GT did the literature search, with arbitration by AC. AM and GT analysed the data and did the figures. GB, AR, SB, HT and CDB interpreted the data. GT and CDB wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest: The authors have no competing financial interests to declare.

FIGURE LEGENDS

Figure 1. The PRISMA flow diagram for search and selection processes of the meta-analysis.

Figure 2. Forest plot and pooled estimates of the effect of NAFLD on the risk of developing new-onset heart failure in 11 eligible cohort studies, stratified by methods used for the diagnosis of NAFLD.

Supplementary Figure 1. (A) Risk of bias graph: review authors' judgments about each domain of the Newcastle-Ottawa scale (NOS) presented as percentages across all included studies. (B) Cochrane risk of bias study-by-study table.

Supplementary Figure 2. Univariable meta-regression analyses. A meta-analysis of the association of age (A), male sex (B), body mass index (C), percentage of pre-existing diabetes (D), percentage of pre-existing hypertension (E), plasma cholesterol concentration (F), White or Caucasian ethnicity (G), and percentage of prior history of acute myocardial infarction (H) with the risk of new-onset HF.

Supplementary Figure 3. Meta-analysis estimates for the 11 eligible studies, given named study is omitted. The effect size was expressed as random-effects HRs and 95% confidence intervals for all eligible studies.

Supplementary Figure 4. Funnel plot of standard error by log-hazard ratio for the risk of developing new-onset HF (n=11 eligible studies). *P*-values by the Egger's regression test.

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Table 1. Eligible cohort studies examining the association between NAFLD and risk of developing incident HF (ordered by publication year; *n*=11 studies).

Author, Year, (Ref.)	Study Characteristics	NAFLD Diagnosis (number of NAFLD patients)	HF Outcomes (number of incident HF events)	Main Findings	Covariate Adjustments
Dhingra R *et al*. 2010 (15)	Community-based cohort (Framingham Heart study): 3,544 United States participants (mean age 44.5 years; white Americans 100%; 1,833 women and 1,711 men; mean BMI 25.9 kg/m^2; pre-existing diabetes 3.8%; pre-existing hypertension 22.5%), who were free of HF and myocardial infarction at baseline. Mean follow-up: 23.6 years	Serum GGT levels (n=1,699)	Incident HF events ((by revision of primary care records and hospitalization records) (n=188)	Participants with a serum GGT level at the median or greater had a higher risk of incident HF (adjusted-HR 1.57, 95% CI 1.02-2.30) compared with those with GGT levels less than the median	Age, sex, body mass index, smoking, systolic blood pressure, treatment for hypertension, alcohol intake, total-to-HDL cholesterol ratio, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, diabetes, valve disease, prior history of myocardial infarction
Wannamethee SG *et al*. 2012 (16)	Community-based cohort (British Regional Heart Study): 3,494 British men aged 60 to 79 years (mean age 68.5 years; predominantly white Europeans [>99%], mean BMI 26.9 kg/m^2; pre-existing diabetes 10.7%; pre-existing hypertension 21.3%), who were free of HF and myocardial infarction at baseline. Mean follow-up: 9 years	Serum GGT levels (n=873)	Incident HF events (by revision of primary care records and hospitalization records) (n=168)	Elevated serum GGT levels (top quartile, ≥38 U/L) were associated with higher risk of incident HF in those aged <70 years (adjusted-HR 1.83, 95%CI 1.02-3.30)	Age, body mass index, smoking, social class, physical activity, alcohol intake, diabetes, systolic blood pressure, antihypertensive treatment, left ventricular hypertrophy, prior stroke, atrial fibrillation, forced expiratory volume in 1 sec, C-reactive protein, leptin, von Willebrand factor, aspartate aminotransferase, alanine aminotransferase, HOMA-insulin resistance, NT-proBNP
Wang Y *et al*. 2013 (17)	Community-based cohort (FINRISK cohort study): 38,079 Finnish participants aged 25-74 years (median age 47 years; predominantly white Europeans; 19,726 women and 18,353 men; mean BMI 27 kg/m^2; pre-existing diabetes 3.2%; pre-existing myocardial infarction 2.4%), who were free of HF at baseline. Mean follow-up: 14.5 years	Serum GGT levels (n=2,739)	Incident HF events (as detected by ICD codes) (n=1,081)	Moderate to high levels of serum GGT (≥90th percentile, i.e. ≥68 U/L) were associated with higher risk of incident HF (adjusted-HR 1.82, 95%CI 1.45-2.29)	Age, sex, body mass index, study area, study year, smoking, education, alcohol intake, physical activity, systolic blood pressure, total cholesterol, valvular heart disease, myocardial infarction, diabetes at baseline and during follow-up

Shah RV *et al*. 2017 (18)	Community-based cohort (Multi-Ethnic Study of Atherosclerosis): 4,234 United States participants aged 45-84 years (mean age 63 years; white or Caucasian 35.5%; 2,011 men and 2,223 women; mean BMI 27.3 kg/m^2; pre-existing diabetes 4.9%; pre-existing hypertension 34.8%; taking hypertension medication 34.8%; taking statins 14.6%), who were free from cardiovascular disease and excessive alcohol intake at baseline. Median follow-up: 12.2 years	Cardiac computed tomography (examined only a single hepatic lobe) (n=719)	Incident HF events (by revision of primary care records and hospitalization records) (n=192)	NAFLD was not associated with higher risk of incident HF (adjusted-HR 1.01, 95%CI 0.86-1.16)	Age, sex, race, body mass index, waist circumference, smoking, physical exercise, HOMA-insulin resistance, C-reactive protein, LDL-cholesterol, diabetes, systolic blood pressure, hypertension medication use, statin medication use, pericardial fat, coronary artery calcium score
Allen AM *et al*. 2019 (19)	Community-based cohort: all adults diagnosed with NAFLD (n=3,869) in Olmsted County (USA) between 1997 and 2014 (median age 53 years; white 87.9%; 1,837 men and 2,032 women; median BMI 33 kg/m^2; pre-existing diabetes 29%; pre-existing cardiovascular disease# 24.3%), and a cohort of 15,209 age- and sex-matched referent individuals without NAFLD (median age 53 years; white 83.5%; 7,236 men and 7,973 women; median BMI 27 kg/m^2; pre-existing diabetes 9.5%; pre-existing cardiovascular disease# 15.1%) Median follow-up: 7.0 years	Hospital International Classification of Diseases Adapted (HICDA) codes (i.e., a system developed at Mayo Clinic for research diagnosis) (n=3,869)	Incident HF events (as detected by Hospital International Classification of Diseases Adapted codes, i.e., a system developed at Mayo Clinic for research diagnosis) (n=861)	NAFLD was associated with higher risk of incident HF (unadjusted-HR 1.47, 95%CI 1.27-1.70)	Age, sex, race, smoking, obesity, dyslipidemia, hypertension, diabetes
Roh JH *et al*. 2020 (20)	308,578 healthy South Korean individuals (mean age 42 years; 152,038 men and 156,540 women; mean BMI 23 kg/m^2) aged >20 years without co-morbidities, who underwent the National Health	Fatty liver index (n=77,145)	Incident HF events (as detected by ICD codes) (n=2,532)	Higher fatty liver index (top quartile, >31) was associated with higher risk of incident HF (adjusted-HR 1.71, 95%CI 1.49-1.96)	Age, sex, smoking, alcohol intake, physical activity, blood pressure, fasting glucose, total cholesterol

	check-ups in the Republic of Korea from 2009 to 2014 (National Health Insurance Service). Median follow-up: 5.4 years				
Lee H *et al*. 2021 (21)	Nationwide health screening database (from the National Health Insurance Service in 2009-2010): 8,962,813 South Korean individuals aged 40-64 years participants (median age 50 years; 4,649,216 men and 4,313,597 women; mean BMI 23.9 kg/m^2; pre-existing diabetes 9.7%; pre-existing hypertension 51%; pre-existing CVD$^{\#}$ 6.3%). Median follow-up: 10.1 years	Fatty liver index (n=2,680,217)	Incident HF events (as detected by ICD-codes) (n=12,432)	NAFLD (defined as fatty liver index ≥30) was associated with higher risk of incident HF (adjusted-HR 1.61, 95%CI 1.55-1.67)	Age, sex, household income quartile, residential area, Charlson comorbidity index, smoking, physical activity, estimated glomerular filtration rate
Fudim M *et al*. 2021 (22)	Retrospective cohort study: 870,535 Medicare beneficiaries from the USA (mean age 74.5 years; white 87%; 375,631 men and 494,904 women; pre-existing diabetes 51.8%; pre-existing hypertension 81.2%; pre-existing myocardial infarction 4.4%). Mean follow-up: 14.3 months	ICD codes (n=27,919)	Incident HF events (as detected by ICD codes) (n=43,667)	NAFLD was associated with higher risk of incident HF (adjusted HR 1.23, 95%CI 1.18-1.29), with a higher risk of developing HF with preserved ejection fraction (adjusted-HR 1.24, 95%CI 1.14-1.34) versus HF with reduced ejection fraction (adjusted-HR 1.09, 95%CI 0.98-1.20)	Age, sex, race, region, hypertension, diabetes, obesity, acute myocardial infarction, atrial fibrillation, chronic kidney disease, valvular disease
Park J *et al*. 2021 (23)	778,739 South Korean individuals without cardiovascular disease and HF aged 40 to 80 years (mean age 53 years; 307,617 men and 471,122 women; mean BMI 24 kg/m^2; pre-existing diabetes 21.9%; pre-existing hypertension 28.3%), who underwent a national health check-up from 2009 to 2012. Median follow-up: 8.5 years	Fatty liver index (n=72,292)	Incident HF events (as detected by ICD codes) (n=29,946)	NAFLD (defined as fatty liver index ≥60) was associated with higher risk of incident HF (adjusted-HR 1.30, 95%CI 1.24-1.36). Among participants with NAFLD, advanced liver fibrosis (assessed by BARD score ≥2) was associated with increased risk for HF (adjusted-HR 1.12, 95%CI 1.04-1.20)	Age, sex, body weight, alcohol intake, smoking, physical activity, income status, hypertension, dyslipidemia, diabetes, estimated glomerular filtration rate

Zou B *et al*. 2021 (24)	Community-based cohort (UK Biobank database): 196,198 individuals (white 97.2%; 92,971 men and 103,227 women; mean age 56.6 years; mean BMI 26.8 kg/m^2; pre-existing hypertension 9.5%; taking hypertension medication 9.4%; taking statins 13.9%) who were free from cardiovascular diseases and excessive alcohol intake. Mean follow-up: 7.9 years	Fatty liver index (n=66,164)	Incident HF events (as detected by ICD codes) (n=1,660)	NAFLD (defined as fatty liver index ≥60) was associated with higher risk of incident HF (unadjusted-HR 1.74, 95%CI 1.63-1.86).	Age, sex, race, assessment center, smoking, Townsend index, systolic blood pressure, non-HDL cholesterol, anti-hypertensive treatment, lipid-lowering treatment, hemoglobin A1c, anti-diabetic treatment
Simon TG *et al*. 2021 (25)	Nationwide histology cohort including all Swedish adults with biopsy-proven NAFLD and without pre-existing cardiovascular disease at baseline (1966-2016, n=10,422; predominantly Caucasian; mean age 52.3 years; 54.8% men; pre-existing diabetes 7.4%). NAFLD patients were matched to ≤5 population controls without NAFLD or cardiovascular disease, by age, sex, calendar year, and county (n=46,517; predominantly Caucasian; mean age 51.2 years; 54% men; pre-existing diabetes 1.6%). Median follow-up: 13.6 years	Liver biopsy (n=10,422)	Incident HF events (as detected by ICD codes) (n=4,988)	NAFLD was associated with higher risk of incident HF (adjusted-HR 1.75, 95% CI 1.63-1.87). Rates of incident HF increased progressively with worsening NAFLD severity, with the highest incidence rates observed with non-cirrhotic fibrosis (adjusted-HR 2.04, 95%CI 1.66-2.51) and cirrhosis (adjusted-HR 2.83, 95%CI 2.08-3.85)	Age, sex, calendar year, residence county, education, number of recorded hospital visits in the 1 year prior to the index date, diabetes, obesity, hypertension, dyslipidemia, chronic kidney disease, family history of premature CHD, statin use, alcohol use disorder during follow-up (defined as a time-varying covariate)

[#]CVD was defined as prior history of myocardial infarction, stroke or heart failure.

Abbreviations: CHD, coronary heart disease; GGT, gamma-glutamyltransferase; HF, heart failure; HOMA, homeostasis model assessment; HR, hazard ratio; ICD, International Classification of Diseases; NAFLD, non-alcoholic fatty liver disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2. Subgroup analyses - Associations between NAFLD and risk of new-onset HF, stratified by study country, median length of follow-up, modality of HF diagnosis, modality of NAFLD diagnosis, or after excluding cohort studies using serum gamma-glutamyltransferase (GGT) levels for diagnosing NAFLD.

	Random-effects Hazard Ratios (95% Confidence Intervals)	*P* values for intergroup differences	Number of studies included	Number of subjects included	I^2-*statistics*
New-onset HF					
Study country					
USA	1.26 (1.08-1.46)	P=0.001	4	897,391	78.2%
Asia	1.52 (1.28-1.80)		3	10,050,130	96.3%
Europe	1.75 (1.67-1.83)		4	294,710	0.0%
Follow-up length					
Follow-up length ≤10 years	1.56 (1.31-1.85)	P=0.572	5	1,306,087	92.9%
Follow-up length >10 years	1.45 (1.23-1.72)		6	9,936,144	96.3%
Modality of HF diagnosis					
No ICD codes	1.33 (0.90-1.98)	P=0.474	3	11,272	71.7%
ICD codes	1.55 (1.38-1.74)		8	11,230,959	95.9%
Modality of NAFLD diagnosis*					
Serum liver enzymes	1.76 (1.46-2.13)	P=0.001	3	45,117	0.0%
Fatty Liver Index	1.57 (1.37-1.81)		4	10,246,328	95.8%
ICD codes	1.33 (1.12-1.58)		2	889,613	80.9%
Imaging techniques	1.01 (0.87-1.17)		1	4,234	ND
Liver biopsy	1.75 (1.63-1.87)		1	56,939	ND
After excluding studies using serum GGT levels					
	1.46 (1.30-1.64)		8	11,197,114	96.3%

*NB: These data are also reported in Fig. 2.