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Author manuscript

*Aliment Pharmacol Ther.* Author manuscript; available in PMC 2024 January 17.

Published in final edited form as:

*Aliment Pharmacol Ther.* 2023 March ; 57(6): 600–609. doi:10.1111/apt.17371.

## Meta-analysis: Chemoprevention of hepatocellular carcinoma with statins, aspirin and metformin

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### SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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## Summary

**Background:** Emerging data suggest that statins, aspirin and metformin may protect against hepatocellular carcinoma (HCC) development. However, prior meta-analyses were limited by heterogeneity and inclusion of studies without adequate adjustment for baseline risks.

**Aim:** To examine by an updated meta-analysis the association between these medications and HCC risk.

**Methods:** Medline and Embase databases were searched from inception to March 2022 for studies that balanced baseline risks between study groups via propensity score matching or inverse probability of treatment weighting, that reported the impact of statins, aspirin or metformin on HCC risk. Multivariable-adjusted hazard ratios (HRs) for HCC were pooled using a random effects model.

**Results:** Statin use was associated with reduced HCC risk overall (HR: 0.52; 95% CI: 0.37–0.72) (10 studies, 1,774,476), and in subgroup analyses for cirrhosis, hepatitis B/C, non-alcoholic fatty liver disease, studies accounting for concurrent aspirin and metformin consumption and lipophilic statins. Aspirin use was associated with reduced HCC risk overall (HR: 0.48; 95% CI: 0.27–0.87) (11 studies, 2,190,285 patients) but not in studies accounting for concurrent statin and metformin use. Metformin use was not associated with reduced HCC risk overall (HR: 0.57; 95% CI: 0.31–1.06) (3 studies, 125,458 patients). Most analyses had moderate/substantial heterogeneity, except in follow-up <60 months for aspirin ( $I^2 = 0\%$ ).

**Conclusion:** Although statin and aspirin use were associated with reduced HCC risk, only statin use was significant in subgroup analyses accounting for concurrent medications. Metformin use was not associated with reduced HCC risk. These data have implications for future clinical trial design.

## 1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.<sup>1,2</sup> Patients with HCC have a 5-year survival of less than 20% overall.<sup>3–7</sup> The poor prognosis of HCC, in general, has led to increased interest in HCC prevention. Emerging data suggest that the use of statins, aspirin and metformin may be chemoprotective against HCC.<sup>8–12</sup> However, prior meta-analyses on this topic had some limitations such as pooling odds ratios that are not time-to-event measurements,<sup>11,13–16</sup> or pooling data that had not been adequately adjusted for background differences in treated versus untreated patients. There have also been several recent relevant large studies that were not included in previous meta-analyses.<sup>17–20</sup>

In light of these considerations, we performed an updated meta-analysis to determine the association between the risk of HCC and the use of statins, aspirin or metformin. We

included cohort studies that balanced patient baseline characteristics between groups by propensity score matching (PSM) or inverse probability of treatment weighting (IPTW) to provide robust estimates of the comparative risk of HCC between study groups.<sup>21–24</sup> We performed a pooled analysis of co-variate-adjusted hazard ratios (HRs) to account for censoring of events and investigated heterogeneity by performing multiple subgroup analyses for relevant factors such as cirrhosis, sex, liver disease aetiology, method of HCC diagnosis, concurrent medication use, follow-up duration and the use of competing risks of death.

## 2 | METHODS

### 2.1 | Search strategy

With reference to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines,<sup>25</sup> a search was conducted on Medline and Embase databases via Ovid for articles relating to the risk of HCC among patients who consumed statins, aspirin and metformin from inception to 10 March 2022. Key search terms included but were not limited to synonyms of ‘Carcinoma, Hepatocellular’, ‘Metformin’, ‘Hydroxymethylglutaryl CoA Reductase Inhibitors’, ‘Aspirin’ and other related terms in the titles and abstracts. The full search strategy is included in Appendix S1. All references were imported into Endnote X9 for the removal of duplicates. We manually screened the bibliographies of included articles for additional relevant data.

### 2.2 | Eligibility and selection criteria

Two pairs of authors (JNY and RWLZ and DJHT and CEF) independently screened abstracts, followed by full-text review to check for study eligibility and inclusion, with discrepancies resolved through consensus from a third independent author (DQH). Only original articles, including prospective and retrospective cohort studies, were considered for inclusion. Cross-sectional studies were excluded from the analysis. Only studies that employed PSM or IPTW to balance patient baseline characteristics between groups were considered for inclusion. The process of matching is designed to minimise selection bias and to achieve balance in baseline characteristics between treatment groups, and existing statistical literature has demonstrated that the resultant effect estimates are empirically equivalent to those of an RCT.<sup>21–23</sup> Systematic reviews, meta-analyses, commentaries and editorials were excluded. Studies inferring results from the same databases were also removed to avoid duplication of the same cohort. Additionally, only articles written or translated into the English language were considered for inclusion. Studies were included if they compared HCC incidence between users of statin, aspirin or metformin versus non-users and reported effect estimates in hazard ratios (HRs) or provided sufficient raw data to allow for calculation of incidental HCC. All the included studies excluded patients with prevalent HCC at the start of the study period. Studies on the paediatric population and animal-related studies were excluded from the analysis.

### 2.3 | Data extraction

Two pairs of authors (CEF and RZWL and JNY and DJHT) independently extracted relevant data from the included articles in blinded pairs. The extracted data comprised of study

characteristics, including but not limited to the author, year, country, geographical region and sample size; patient characteristics including age, gender, race, comorbidities such as hypertension (HTN), type 2 diabetes mellitus (DM), hyperlipidemia (HLD), smoking, cirrhosis and aetiologies of liver disease such as hepatitis B virus (HBV), hepatitis C virus (HCV) and non-alcoholic fatty liver disease (NAFLD). The primary outcome of interest was the comparative risk of HCC with statin, aspirin or metformin use compared with non-users. Co-variate adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for HCC incidence in patients receiving statin, aspirin or metformin versus non-users were recorded. The co-variables included in multivariable models or PSM were also extracted across studies. In studies that only reported median and interquartile ranges, we conducted the transformation of values into mean and standard deviations via the widely adopted formulas by Wan et al.<sup>26</sup>

## 2.4 | Statistical analysis

All analyses were conducted in R Studio (Version 4.1.2) using the *meta* package, and statistical significance was considered for outcomes with a  $p < 0.05$ . Statistical heterogeneity was assessed via  $I^2$  and Cochran  $Q$  test values, where an  $I^2$  value of  $<50\%$ ,  $50\%–75\%$  and  $>75\%$  represented low, moderate and a high degree of heterogeneity respectively.<sup>27,28</sup> Random effect models were used in all analyses regardless of heterogeneity scores, as it has been shown to provide more robust estimates compared to fixed effects models.<sup>29</sup> To compare HCC incidence between patients receiving statin, aspirin or metformin versus non-users, hazard ratios (HRs) were pooled via the inverse variance method using the DerSimonian and Laird random effects model.<sup>30</sup> Analysis was stratified based on the drug class the patient received (statin, aspirin or metformin). Where sufficient studies were available, pre-specified subgroup and sensitivity analysis based on the aetiology of liver disease (i.e HBV, HCV, NASH and alcohol-associated liver disease), the presence of cirrhosis, sex, verification of HCC diagnosis by imaging or histology (versus relying on International Classification of Diseases [ICD] codes), whether studies accounted for concurrent hepatoprotective medications (by either stratified analysis or adjusted multivariable Cox regression analysis), by study follow-up duration, and for studies that accounted for competing risks of mortality without HCC. Further subgroup analyses were conducted for the type of statins (lipophilic versus hydrophilic). Lipophilic statins included atorvastatin, simvastatin, fluvastatin and lovastatin, while hydrophilic statins included pravastatin and rosuvastatin.

## 2.5 | Quality assessment and publication bias

Quality assessment of included articles was done with the Joanna Briggs Institute (JBI) critical appraisal checklist for prevalence studies, which rates the risk of bias of cohort studies on the premises of appropriateness of sample frame, sampling method, adequacy of sample size, data analysis, methods for identification and measurement of relevant conditions, statistical analysis and response rate adequacy.<sup>31</sup> Studies were characterised as having high (JBI checklist score 1–3), moderate (4–6) or low (7–9) risk of bias. Publication bias was assessed for outcomes where sufficient studies were involved in the analysis ( $n \geq 10$ ) (Appendix S4), via visual inspection of funnel plots for asymmetry and with Egger's test.<sup>32</sup>

## 3 | RESULTS

### 3.1 | Summary of included articles

A systematic search of the literature using the previously mentioned search strategy yielded 1848 articles after the removal of duplicates. After 1750 articles were excluded based on the study title and abstract, 98 articles were selected for full-text review, of which 21 articles met the inclusion criteria. Two additional articles were retrieved for full-text review after screening references of included articles, and a total of 23 articles were included in the final analysis (Figure 1). In total, nine articles originated from Taiwan,<sup>17,19,33–39</sup> five from Korea,<sup>18,40–43</sup> three from Hong Kong,<sup>44–46</sup> three from the United States,<sup>20,47,48</sup> two from Sweden,<sup>49,50</sup> and one from the United Kingdom.<sup>51</sup> Five studies used IPTW and the remaining 18 studies conducted PSM to adjust for confounding baseline characteristics. The key characteristics and quality assessment for the included articles are summarised in Appendix S2. A total of 4,090,219 individuals were included, comprising 1,774,476 individuals in the analysis for statins, 2,190,285 patients in the analysis for aspirin, and 125,458 individuals in the analysis for metformin. There were a total of 34,422 incident cases of HCC in the included studies. All studies were assessed to have a low ( $n = 18$ ) to moderate ( $n = 5$ ) risk of bias based on the JBI appraisal tool.

### 3.2 | Statin use and HCC risk

**3.2.1 | Overall**—A pooled analysis of 10 studies and 1,774,476 patients determined that the overall risk of HCC incidence in statin users was lower (HR: 0.52; 95% CI: 0.37–0.72;  $p < 0.01$ ;  $I^2 = 97.80\%$ ) compared to non-users (Table 1, Appendix S3).

**3.2.2 | By sex**—Statin usage was associated with reduced HCC risk in males (HR: 0.45; 95% CI: 0.24–0.85;  $p = 0.01$ ) (2 studies, 115,411 patients), but not in females (HR: 0.50; 95% CI: 0.22–1.17;  $p = 0.11$ ) (2 studies, 115,411 patients). However, there was no significant subgroup difference ( $p = 0.83$ ).

**3.2.3 | By aetiology of liver disease**—Statin use was associated with reduced HCC incidence among patients with HBV, (HR: 0.53; 95% CI: 0.32–0.88;  $p = 0.01$ ) (5 studies, 152,716 patients), HCV (HR: 0.79; 95% CI: 0.64–0.99;  $p = 0.04$ ) (3 studies, 16,058 patients) and NAFLD (HR: 0.68; 95% CI: 0.59–0.77;  $p < 0.01$ ) (2 studies, 242,751 patients).

**3.2.4 | By the presence of cirrhosis**—Among patients with cirrhosis, statin use was associated with a reduced risk of HCC (HR: 0.95; 95% CI: 0.91–0.99;  $p = 0.04$ ) (3 studies, 21,584 patients).

**3.2.5 | Studies that accounted for competing risk of death without HCC**—Statin usage was associated with reduced HCC risk (HR: 0.51; 95% CI: 0.32–0.81;  $p < 0.01$ ) in studies that accounted for competing risk of death without HCC (5 studies, 980,486 patients).

**3.2.6 | Confirmation of HCC diagnosis**—Statin usage was associated with reduced HCC incidence in studies that relied on ICD codes for HCC diagnosis (HR: 0.49; 95%

CI: 0.31–0.78;  $p < 0.01$ ) (8 studies, 1,708,031 patients), but not in studies that verified the presence of HCC by imaging or histology (HR: 0.60; 95% CI: 0.33–1.09;  $p = 0.09$ ) (2 studies, 66,445 patients).

**3.2.7 | Studies that accounted for concurrent aspirin, NSAID and metformin use**—In our pooled analysis of the nine studies involving 1,534,926 patients accounted for the use of aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and metformin, statin use continued to be associated with reduced HCC incidence compared to non-users (HR: 0.52; 95% CI: 0.37–0.75;  $p < 0.01$ ).

**3.2.8 | Lipophilic versus hydrophilic statins**—Lipophilic statin users had a significantly lower risk of HCC incidence compared to non-users (HR: 0.46; 95% CI: 0.37–0.57;  $p < 0.01$ ) (3 studies, 1,083,952 patients), but not hydrophilic statin users (HR: 0.48; 95% CI: 0.18–1.27;  $p = 0.14$ ) (3 studies, 1,083,952 patients).

**3.2.9 | Mean follow-up duration**—Statin usage was associated with reduced HCC incidence in studies with a mean follow-up duration shorter than 60 months (HR: 0.49; 95% CI: 0.39–0.62;  $p < 0.01$ ), and in studies with a mean follow-up duration of 60 months or longer (HR: 0.67; 95% CI: 0.49–0.92;  $p = 0.01$ ), with no significant subgroup difference ( $p = 0.10$ ).

### 3.3 | Aspirin use and HCC risk

**3.3.1 | Overall**—Pooled analysis of 11 articles and 2,190,285 patients determined a lower risk of HCC in aspirin users compared to non-users (HR: 0.48; 95% CI: 0.27–0.87;  $p = 0.01$ ;  $I^2 = 99.50\%$ ) (Table 2, Appendix S3).

**3.3.2 | By sex**—Aspirin usage was associated with reduced HCC risk in males (HR: 0.78; 95% CI: 0.67–0.90;  $p < 0.01$ ) (3 studies, 365,231 patients), but not in females (HR: 0.71; 95% CI: 0.48–1.04;  $p = 0.08$ ) (3 studies, 365,231 patients).

**3.3.3 | By aetiology of liver disease**—Aspirin use was associated with reduced HCC risk in patients with HCV (HR: 0.69; 95% CI: 0.59–0.80;  $p < 0.01$ ) (3 studies, 48,255 patients), but not in those with HBV (HR: 0.45; 95% CI: 0.12–1.60;  $p = 0.18$ ) (5 studies, 97,848 patients).

**3.3.4 | By the presence of cirrhosis**—Among patients with cirrhosis, aspirin use was associated with a significant reduction in HCC risk (HR: 0.68; 95% CI: 0.51–0.91;  $p = 0.01$ ) (5 studies, 46,526 patients).

**3.3.5 | Studies that accounted for competing risk of death without HCC**—In a pooled analysis of the six studies involving 142,281 patients which accounted for the competing risk of death without HCC, aspirin use was not associated with a reduced risk of HCC (HR: 0.50; 95% CI: 0.18–1.36;  $p = 0.17$ ).

**3.3.6 | Confirmation of HCC diagnosis**—In studies that relied on ICD codes for HCC diagnosis (7 studies, 2,131,378 patients), aspirin use was associated with significantly



reduced HCC risk (HR: 0.66; 95% CI: 0.54–0.82;  $p < 0.01$ ), but not in studies that verified the diagnosis of HCC by imaging or histology (HR: 0.28; 95% CI: 0.06–1.19;  $p = 0.08$ ) (4 studies, 58,907 patients).

**3.3.7 | Studies that accounted for a concurrent statin, NSAID and metformin use**—In studies that did not account for concurrent use of metformin, NSAIDs and statins, aspirin use was associated with reduced HCC risk (HR: 0.42; 95% CI: 0.27–0.64;  $p < 0.01$ ) (3 studies, 1,697,000 patients). However, in studies that accounted for concurrent use of metformin, NSAIDs and statins, aspirin use was not associated with reduced HCC risk (HR: 0.53; 95% CI: 0.23–1.21;  $p = 0.13$ ) (8 studies, 493,285 patients).

**3.3.8 | Mean follow-up duration**—Aspirin usage was associated with reduced HCC incidence in studies with a mean follow-up duration shorter than 60 months (HR: 0.74; 95% CI: 0.63–0.87;  $p < 0.01$ ) and in studies with a mean follow-up duration longer than 60 months (HR: 0.69; 95% CI: 0.63–0.75;  $p < 0.01$ ), with no significant subgroup difference ( $p = 0.93$ ).

### 3.4 | Metformin use and HCC risk

From a pooled analysis of three articles and 125,458 patients, metformin use was not associated with a lower risk of HCC versus non-users (HR: 0.57; 95% CI: 0.31–1.06;  $p = 0.08$ ;  $I^2 = 95.90\%$ ) (Table 3, Appendix S3).

**3.4.1 | Confirmation of HCC diagnosis**—All included studies in the pooled analysis of metformin use and HCC risk used ICD codes to verify HCC diagnosis. In these studies, the risk of HCC was comparable between metformin users and non-users (HR: 0.57; 95% CI: 0.31–1.06;  $p = 0.08$ ).

**3.4.2 | Studies that accounted for a concurrent statin, NSAID, and aspirin use**—In studies that accounted for a concurrent statin, NSAID, and aspirin use, metformin use was not associated with the risk of HCC (HR: 0.97; 95% CI: 0.60–1.58;  $p = 0.91$ ) (2 studies, 101,611 patients).

### 3.5 | Heterogeneity and publication bias

There was a moderate to high degree of heterogeneity in all analyses for the association between statin use and HCC risk, except in subgroup analysis for follow-up time <60 months ( $I^2 = 49.5\%$ ,  $p = 0.12$  for heterogeneity). Likewise, there was a moderate to high degree of heterogeneity in all analyses for the association between aspirin use and HCC risk, except in the subgroup analysis for the male sex ( $I^2 = 0\%$ ,  $p = 0.39$  for heterogeneity), and analyses for follow-up duration (all  $I^2 = 0\%$ , and  $p > 0.34$  for heterogeneity). There was a high degree of heterogeneity in all analyses for the effect of metformin use on HCC risk. Egger's test for publication bias was significant for statins ( $p = 0.026$ ), although no significant publication bias was detected in the overall analysis of aspirin ( $p = 0.671$ ). However, visual inspection of funnel plots was suggestive of publication bias in the overall analysis for both statins and aspirin due to the asymmetrical distribution of data points

across the vertical axis (Appendix S4). There were insufficient studies included in the analysis for metformin for publication bias to be assessed.

## 4 | DISCUSSION

### 4.1 | Main findings

In this systematic review and meta-analysis of 23 moderate–high-quality matched studies involving 4,090,219 individuals, we determined that statin and aspirin use were all associated with a substantial reduction in HCC risk in the overall analyses, while metformin was not associated with reduced HCC risk. The strongest association with HCC risk reduction appeared to be among statin users, where the reduction of HCC risk persisted in multiple subgroup analyses, including studies that accounted for concurrent use of aspirin and metformin by either stratified analysis or adjusted multivariable analysis. By contrast, data for aspirin and metformin were limited, and the association between aspirin or metformin use and HCC risk persisted in fewer/none of the subgroup analyses and did not reach statistical significance in subgroup analyses that accounted for concurrent statin use. These data suggest that statins may have an important role in the chemoprevention of HCC but require validation in randomised controlled trials before routine use in clinical practice.

Statin use was associated with reduced HCC risk in most of the subgroup analyses such as those with cirrhosis, HBV, HCV, NAFLD, male sex, follow-up duration, studies that accounted for competing risks of death without HCC and studies that accounted for concurrent use of aspirin, NSAIDs and metformin. Notably, lipophilic statins, but not hydrophilic statins were associated with a reduction in HCC risk. There was no significant reduction in HCC risk among females, which may be related to the lower background risk of HCC in this subgroup. There was moderate to severe heterogeneity in most of the analyses for statins, calling for caution when interpreting these data. However, there was no significant heterogeneity in the subgroup analysis for study follow-up <60 months, suggesting that follow-up duration was a major source of heterogeneity.

Aspirin use was associated with a significant reduction in HCC risk in subgroup analyses for patients with cirrhosis, HCV, males and among studies that did not verify HCC risk with imaging or histology. Notably, aspirin was associated with reduced HCC risk in studies that did not account for concurrent use of statins, NSAIDs and metformin, but not among studies that accounted for concurrent use of these medications by either stratified analysis or adjusted multivariable analysis. This calls for a cautious interpretation of the overall analyses of the association between aspirin and HCC risk. There was moderate to severe heterogeneity in the overall and all the subgroup analyses, except the analyses for male sex and follow-up duration.

Metformin use was not associated with a significant reduction in HCC risk in the overall analysis. There was also no significant association with reduced HCC risk among studies which accounted for concurrent medication use by stratified or adjusted multivariable analyses. Overall, the data for the association between metformin use and HCC risk appeared to be less robust.



## 4.2 | In context with current literature

The current study provides a detailed, updated analysis of the existing literature, with multiple additional subgroup analyses that provide confidence for the potential benefits of statins and inform clinical trial design. Some of the previous meta-analyses were limited by the use of odds ratios<sup>13,14,16,52</sup> for HCC risk, lack of PSM or IPTW analyses to balance baseline characteristics between study groups,<sup>11,16,53</sup> or did not thoroughly investigate sources of heterogeneity through detailed subgroup analyses.<sup>11,54,55</sup> A recent meta-analysis focusing on aspirin use and HCC risk pooled HRs after propensity score matching and determined similar findings (HR 0.54), although only 4 studies were included.<sup>12</sup> In contrast, we pooled adjusted hazard ratios that account for censoring of events and were adjusted for co-variates, included only moderate to high-quality studies that performed balancing of baseline characteristics for HCC risk, and performed extensive subgroup analyses to identify sources of heterogeneity.

## 4.3 | Limitations

The current study is not without limitations. All included studies were observational, and hence subject to confounding and bias, such as immortal time bias and indication bias. Though each study attempted to balance the baseline characteristics between groups, residual confounders, such as family history or fibrosis stage, may not have been accounted for. There was potential publication bias in the overall analyses for aspirin and statin use. In addition, several of the subgroup analyses were limited by a small number of included studies, and there were insufficient studies for subgroup analyses for NAFLD in the analyses of HCC risk in aspirin or metformin.

## 5 | CONCLUSION

Statin and aspirin use were all associated with a substantial reduction in HCC risk in the overall analyses, while metformin use was not associated with reduced HCC risk. The strongest association with HCC risk reduction appeared to be among statin users, where the association with reduced HCC risk persisted in multiple subgroup analyses including for studies that accounted for concurrent use of aspirin and metformin. By contrast, subgroup data for metformin were limited, and the association between aspirin or metformin use and HCC risk reduction was not statistically significant in subgroup analyses for studies that accounted for concurrent statin use. These data have implications for future clinical trial design.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENTS

*Declaration of personal interests:* All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. No writing assistance was obtained in the preparation of the manuscript. The manuscript, including related data, figures and tables has not been previously published and the manuscript is not under consideration elsewhere.

## FUNDING INFORMATION

No external funding was required for this study.

## CONFLICT OF INTEREST

MHN: Research support: Pfizer, Enanta, Gilead, Exact Sciences, Vir Biotech, Helio Health, National Cancer Institute, Glycotest, B.K. Kee Foundation. Consulting and/or Advisory Board: Intercept, Exact Science, Gilead, GSK, Eli Lilly, Laboratory of Advanced Medicine, Janssen. R.L. receives funding support from NIAAA (U01AA029019), NIEHS (5P42ES010337), NCATS (5UL1TR001442), NIDDK (U01DK130190, U01DK061734, R01DK106419, P30DK120515, R01DK121378, R01DK124318), NHLBI (P01HL147835) and DOD PRCRP (W81XWH-18-2-0026). RL serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institutions received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc. D.H. receives funding support from Singapore Ministry of Health's National Medical Research Council under its NMRC Research Training Fellowship (MOH-000595-01). In addition, he has served as an advisory board member for Eisai. The other authors declare no conflict of interest.

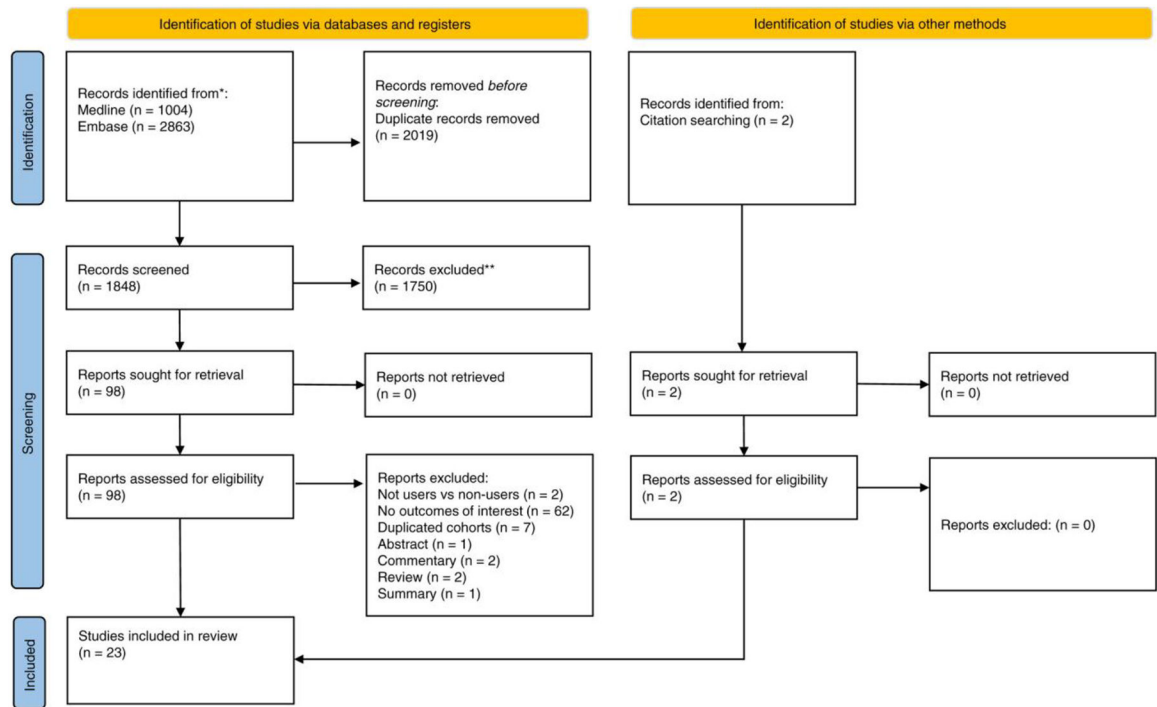
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**FIGURE 1.**  
PRISMA flowchart.



TABLE 1

## Hepatocellular carcinoma risk among statin users

	No. of studies	Sample size	HR	95% confidence interval	p value	I <sup>2</sup> (%)	p value for Cochran Q test of heterogeneity	Subgroup difference
Statins								
Overall	10	1,774,476	0.52	0.37–0.72	<0.01*	97.80	<0.01	
Cirrhosis	3	21,534	0.95	0.91–0.99	<b>0.04</b> *	90.20	<0.01	
Hepatitis B	5	152,716	0.53	0.32–0.88	<b>0.01</b> *	96.70	<0.01	
Hepatitis C	3	16,058	0.79	0.64–0.99	<b>0.04</b> *	81.70	<0.01	
NAFLD	2	242,751	0.68	0.59–0.77	<0.01*	90.80	<0.01	
Accounted for competing risk of death without HCC	5	980,486	0.51	0.32–0.81	<0.01*	97.50	<0.01	
Sex								
Male	2	115,411	0.45	0.24–0.85	<b>0.01</b> *	85.90	<0.01	0.83
Female	2	115,411	0.50	0.22–1.17	0.11	75.00	0.01	
HCC diagnosis method								
Verified by imaging/histology	2	66,445	0.60	0.33–1.09	0.09	95.10	<0.01	0.59
ICD codes	8	1,708,031	0.49	0.31–0.78	<0.01*	98.60	<0.01	
Statin type								
Lipophilic	3	1,083,952	0.46	0.37–0.57	<0.01	64.00	0.06	0.93
Hydrophilic	3	1,083,952	0.48	0.18–1.27	0.14	99.10	<0.01	
Accounted for concurrent use of aspirin, NSAIDs and metformin								
Yes	9	1,534,926	0.52	0.37–0.75	<0.01*	98.10	<0.01	
Mean follow-up duration								
<60 months	4	814,691	0.49	0.39–0.62	<0.01*	49.50	0.12	0.10
60 months	4	965,093	0.67	0.49–0.92	<b>0.01</b> *	96.20	<0.01	

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; NAFLD, non-alcoholic fatty liver disease; ICD, International Classification of Diseases; HR, hazard ratio; I<sup>2</sup>, level of heterogeneity.

\* Bolded p < 0.05 denotes statistical significance.

TABLE 2

## Hepatocellular carcinoma risk among aspirin users

	No. of studies	Sample size	HR	95% confidence interval	<i>p</i> value	<i>I</i> <sup>2</sup> (%)	<i>p</i> value for Cochran <i>Q</i> test of heterogeneity	Subgroup difference
Aspirin								
Overall	11	2,190,285	0.43	0.27–0.87	<b>0.01</b> *	99.50	0.00	
Cirrhosis	5	46,526	0.68	0.51–0.91	<b>0.01</b> *	84.90	<0.01	
Hepatitis B	5	97,643	0.45	0.12–1.60	0.22	99.80	<0.01	
Hepatitis C	3	43,255	0.69	0.59–0.80	<b>&lt;0.01</b> *	50.20	0.13	
Accounted for competing risk of death without HCC	6	142,281	0.50	0.18–1.36	0.17	99.70	<0.01	-
Sex								
Male	3	365,231	0.79	0.67–0.90	<b>&lt;0.01</b> *	0.00	0.39	0.66
Female	3	365,231	0.71	0.46–1.04	0.08	67.00	0.05	
HCC diagnosis method								
Verified by imaging/histology	4	58,907	0.28	0.06–1.19	0.08	99.80	<0.01	0.24
ICD codes	7	2,131,378	0.66	0.54–0.82	<b>&lt;0.01</b> *	93.40	<0.01	
Accounted for concurrent use of statins, NSAIDs and metformin								
Yes	8	493,285	0.53	0.23–1.21	0.13	99.60	<0.0	0.60
No	3	1,697,000	0.42	0.27–0.64	<b>&lt;0.01</b> *	93.40	<0.01	
Mean follow-up duration								
<60 months	2	42,545	0.74	0.63–0.87	<b>&lt;0.01</b> *	0.00	0.35	0.93
60 months	2	1,134,408	0.69	0.63–0.75	<b>&lt;0.01</b> *	0.00	0.89	

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; ICD, International Classification of Diseases; HR, hazard ratio; *I*<sup>2</sup>, level of heterogeneity.

\* Bolded *p* < 0.05 denotes statistical significance

**TABLE 3**

## Hepatocellular carcinoma risk in metformin users

	No. of studies	Sample size	HR	95% confidence interval	<i>p</i> value	<i>I</i> <sup>2</sup> (%)	<i>p</i> value for Cochran <i>Q</i> test of heterogeneity	Subgroup difference
Metformin								
Overall	3	125,458	0.57	0.31–1.06	0.03	95.90	<0.01	
Confirmation of HCC diagnosis								
ICD codes	3	125,458	0.57	0.31–1.06	0.08	95.90	<0.01	
Accounted for use of statins, aspirin and NSAIDs								
Yes	2	101,611	0.97	0.60–1.58	0.91	95.70	<0.01	
Mean follow-up duration								
<60 months	2	67,647	0.23	0.02–2.71	0.24	96.00	<0.01	
60 months	1	-						

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; ICD, International Classification of Diseases; HR, hazard ratio; *I*<sup>2</sup>, level of heterogeneity.