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SYSTEMATIC REVIEWS AND META-ANALYSES

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An Observational Data Meta-analysis on the Differences in Prevalence and Risk Factors Between MAFLD vs NAFLD

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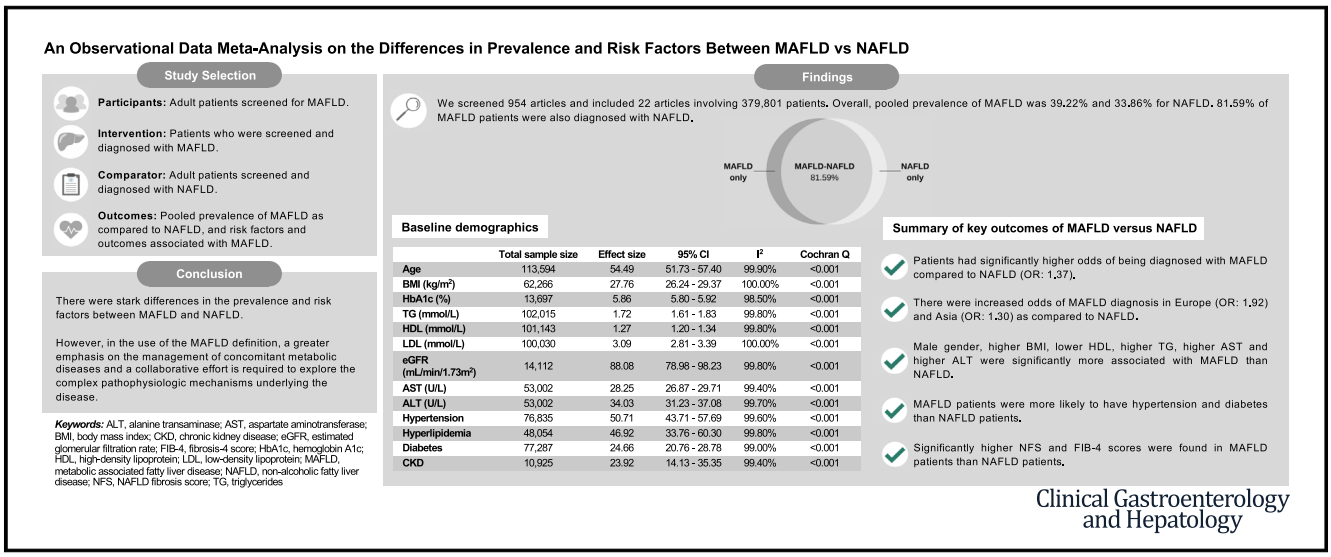

	Total sample size	Effect size	95% CI	I^2	Cochran Q
Age	113,594	54.49	51.73 - 57.40	99.90%	<0.001
BMI (kg/m^2)	62,266	27.76	26.24 - 29.37	100.00%	<0.001
HbA1c (%)	13,697	5.86	5.80 - 5.92	98.50%	<0.001
TG (mmol/L)	102,015	1.72	1.61 - 1.83	99.80%	<0.001
HDL (mmol/L)	101,143	1.27	1.20 - 1.34	99.80%	<0.001
LDL (mmol/L)	100,030	3.09	2.81 - 3.39	100.00%	<0.001
eGFR (mL/min/1.73m^2)	14,112	88.08	78.98 - 98.23	99.80%	<0.001
AST (U/L)	53,002	28.25	26.87 - 29.71	99.40%	<0.001
ALT (U/L)	53,002	34.03	31.23 - 37.08	99.70%	<0.001
Hypertension	76,835	50.71	43.71 - 57.69	99.60%	<0.001
Hyperlipidemia	48,054	46.92	33.76 - 60.30	99.80%	<0.001
Diabetes	77,287	24.66	20.76 - 28.78	99.00%	<0.001
CKD	10,925	23.92	14.13 - 35.35	99.40%	<0.001

BACKGROUND & AIMS: **The shift to redefine nonalcoholic fatty liver disease (NAFLD) as metabolic associated fatty liver disease (MAFLD) can profoundly affect patient care, health care professionals, and progress within the field. To date, there remains no consensus on the characterization of NAFLD vs MAFLD. Thus, this study sought to compare the differences between the natural history of NAFLD and MAFLD.**

METHODS: **Medline and Embase databases were searched to include articles on prevalence, risk factors, or outcomes of patients with MAFLD or NAFLD. Meta-analysis of proportions was conducted using the generalized linear mix model. Risk factors and outcomes were evaluated in conventional pairwise meta-analysis.**

[a]Authors share co-first authorship. [b]Authors share co-senior authorship.

Abbreviations used in this article: **ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HbA1c, Hemoglobin A1c; HDL, high-density lipoprotein; JBI, Joanna Briggs Institute; LDL, low-density lipoprotein; MAFLD, metabolic associated fatty liver disease; MD, mean difference; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD Fibrosis Score; OR, odds ratio; TG, triglycerides.**

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RESULTS: **Twenty-two articles involving 379,801 patients were included. Pooled prevalence of MAFLD was 39.22% (95% confidence interval [CI], 30.96%–48.15%) with the highest prevalence in Europe and Asia, followed by North America. The current MAFLD Definition only accounted for 81.59% (95% CI, 66.51%–90.82%) of NAFLD diagnoses. Patients had increased odds of being diagnosed with MAFLD compared with NAFLD (odds ratio, 1.37; 95% CI, 1.16–1.63; $P < .001$). Imaging modality resulted in a significantly higher odds of being diagnosed with MAFLD compared with NAFLD, but not biopsy. MAFLD was significantly associated with males, higher body mass index, hypertension, diabetes, lipids, transaminitis, and greater fibrosis scores compared with NAFLD.**

CONCLUSIONS: **There were stark differences in the prevalence and risk factors between MAFLD and NAFLD. However, in the use of the MAFLD Definition, a greater emphasis on the management of concomitant metabolic diseases and a collaborative effort is required to explore the complex pathophysiologic mechanisms underlying the disease.**

Keywords: Liver Diseases; Metabolic Associated Fatty Liver Disease; Nonalcoholic Fatty Liver Disease; Prevalence; Risk Factors.

Nonalcoholic fatty liver disease (NAFLD) is an evolving pandemic over the decades, accounting for 25% of prevalence of the global population, with a higher prevalence (42%) described in Southeast Asia.[1] NAFLD is currently described as the presence of steatosis in $\geq$5% of hepatocytes in the absence of a secondary cause of hepatic steatosis.[2,3] Nonalcoholic steatohepatitis, a clinically aggressive variant of NAFLD, is histologically defined as hepatic steatosis in the presence of hepatocyte injury (ballooning) and inflammation with or without fibrosis.[4,5] NAFLD is commonly associated with metabolic dysfunction,[4,6] can result in the development of cardiovascular disease[7] and hepatocellular carcinoma,[8] and is the most fastest growing etiology of chronic liver failure requiring liver transplantation.[9] Although NAFLD is strongly associated with obesity, the presence of lean NAFLD or patients with NAFLD with body mass index (BMI) $<$25 kg/m^2 can also occur in 5.1% of the general population.[10]

Recently, there has been an effort to redefine NAFLD to better reflect the underlying disease pathology and its close correlation with metabolic comorbidities. Two international consensus position statements have called for a change of name to "metabolic associated fatty liver disease" (MAFLD).[11,12] Unlike NAFLD, which is based on the exclusion of other etiologies of fatty liver, the diagnosis of MAFLD is a positive inclusion that correlates with the metabolic risk profile of the patient.[13] The current consensus describes MAFLD as a multisystem disorder with the presence of hepatic steatosis and 1 of the 3 features including: (1) overweight or obesity, (2) type 2 diabetes mellitus, or (3) lean or normal weight with evidence of metabolic dysregulation.[14] Although the proposed change in Definition appears subtle, the resultant effect can have major implications that can affect our current understanding of prevalence and risk factors. Furthermore, such a change in diagnostic criteria can affect the regulatory landscape, which inclusion has largely been based on the definition of nonalcoholic steatohepatitis.[15]

The question thus remains if the characterization of NAFLD and MAFLD is interchangeable. Both the American Association for the Study of Liver Diseases and the European Association for the Study of Liver Diseases (EASL) currently have not endorsed the proposed Definition of MAFLD.[1] Although several observational studies have emerged examining the differences between NAFLD and MAFLD,[16–18] varying opinions and results have emerged from the literature. Hence, we sought to compare the differences between the natural history of NAFLD and MAFLD, specifically in the variations on the prevalence, risk factors, and outcomes between the 2 definitions.

Methods

Search Strategy

This review was registered with PROSPERO. With reference to the Preferred Reporting Items for Systematic Review and Meta-Analyses 2020 (Supplementary Appendix 1 and Supplementary Material 2) and Meta-analysis Of Observational Studies in Epidemiology guidelines,[19,20] 2 electronic databases, Medline and Embase, were searched for articles describing the prevalence, risk factors, and outcomes of patients with both MAFLD and NAFLD from inception to September 17, 2021. Key search terms such as "metabolic associated fatty liver disease" and "metabolic associated steatohepatitis" were used in the search strategy. The search strategy used was: ((Metabol* adj2 associat* fatty liver diseas*) or MAFLD).tw. or ((mash or (metabol* adj2 steatohepatitis)) and (hepatic or liver)).tw. References were imported into Endnote X9 for duplicate removal. References of the included articles were manually screened to ensure no studies were missed.

Eligibility and Selection Criteria

Four authors (G.E.H.L., A.T., Y.H.C., and C.H.N.) independently performed the title abstract sieve and full text

reviews, excluding articles based on the eligibility criteria. Any discrepancies were resolved by consensus or in consultation with a fifth independent author (M.D.M.). Only original articles written or translated into the English language were included in this review. Reviews, abstracts, commentaries, letters, and editorials were excluded. Duplicate studies inferring results from the same databases were also removed. Only observational studies that described the prevalence, associated risk factors, or outcomes of patients with MAFLD or NAFLD were included. Studies using Fatty Liver Index for the diagnosis of MAFLD were excluded from the analysis. Studies conducted on the pediatric population were also excluded.

What You Need to Know

Background

The shift to redefine nonalcoholic fatty liver disease (NAFLD) as metabolic associated fatty liver disease (MAFLD) entails major implications. This study sought to compare differences between NAFLD and MAFLD.

Findings

MAFLD was significantly associated with males, higher body mass index, hypertension, diabetes, higher triglycerides, lower high-density lipoprotein, higher liver enzymes, and greater fibrosis scores compared with NAFLD.

Implications for patient care

This study demonstrates stark differences in the natural history of MAFLD and NAFLD. Greater emphasis should be placed on the management of comorbidities in patients with MAFLD.

Definition and Data Extraction

Two pairs of authors (G.E.H.L. and A.T., Y.H.C. and C.H.N.) independently extracted relevant data from included articles including but not limited to author, year, country, geographical region, diagnostic modality, and patient characteristics, such as sample size, age, gender, ethnicity, metabolic parameters (ie, BMI, hemoglobin A1c [HbA1c], high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides [TG]), presence of comorbidities (ie, diabetes, hypertension, and hyperlipidemia), estimated glomerular filtration rate, liver enzymes (ie, aspartate aminotransferase [AST], alanine transaminase [ALT]), and fibrosis parameters (ie, NAFLD Fibrosis Score [NFS] and Fibrosis-4 score). MAFLD was diagnosed according to the criteria proposed by the international expert panel.[11] The criteria includes presence of fatty liver with concomitant type 2 diabetes, overweight or obesity (ie, BMI $\geq$23 kg/m^2), or 2 or more of the following metabolic conditions: (1) waist circumference $\geq$90 cm in men and $\geq$80 cm in women (central obesity), (2) blood pressure $\geq$130/85 mm Hg or receiving antihypertensives, (3) plasma triglycerides $\geq$1.7 mmol/L or receiving specific drug treatment, (4) plasma HDL-cholesterol $<$1.0 mmol/L in men and $<$1.3 mmol/L in women, (5) prediabetes (fasting plasma glucose 5.6–6.9 mmol/L or HbA1c 5.7%–6.4%), and homeostatic model assessment for insulin resistance score $\geq$2.5. NAFLD was diagnosed according to the EASL-European Association for the Study of Diabetes-European Association for the Study of Obesity and American Association for the Study of Liver Diseases Clinical Practice Guidelines for the Management of NAFLD: (1) fatty liver by abdominal ultrasonography, (2) alcohol consumption no more than 30 g/day for men and 20 g/day for women, and (3) no competing etiologies for fatty liver or coexisting causes of chronic liver disease.[2] Individuals with MAFLD or NAFLD included those with overlapping MAFLD and NAFLD. HDL, LDL, and TG were reported in millimoles per liter (mmol/L), whereas liver enzymes were reported in units per liter (U/L). Transformation of values were carried out using pre-existing formulae, in which mean and standard deviations were estimated from median and range using the widely adopted formula by Wan et al.[21] Blinded checking of the data by the authors was conducted to ensure accuracy of the data extracted, with discrepancies in data resolved through consensus.

Quality Assessment

Quality assessment of included articles was conducted by 4 independent authors (W.H.L. and D.T., J.X. and J.N.Y.) with the Joanna Briggs Institute (JBI) Critical Appraisal Tool.[22] The JBI assessment 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. Disagreements were resolved by consensus or appeal to a fifth author (M.D.M.). Publication bias was assessed by visual inspection of the respective funnel plots.[23]

Statistical Analysis

All analysis was done in R studio (Ver: 1.3.1093) and Stata (Ver: 16.1 StataCorp LLC).[24] Statistical significance was considered for outcomes with a P value $\leq$ .0500. The proportion of individuals with MAFLD and NAFLD in each study was combined to give an overall pooled prevalence of MAFLD and NAFLD, respectively, using the generalized linear mix model with Clopper Pearson interval.[25,26] Subgroup analysis was subsequently conducted to stratify prevalence by diagnostic modality (imaging vs biopsy) and geographical region (North

America, Europe, and Asia) to explore potential sources of heterogeneity. Additionally, baseline characteristics of patients with MAFLD were pooled to obtain the effect size for continuous and dichotomous data with log transformation where applicable. To compare associated risk factors and outcomes between MAFLD and NAFLD, pairwise meta-analysis was conducted in DerSimonian and Laird to obtain the odds ratios (ORs) and mean differences (MDs) for dichotomous and continuous variables, respectively, and corresponding 95% confidence intervals (CIs). Statistical heterogeneity was assessed via I^2 and Cochran Q test values, where an I^2 value of 25%, 50%, and 75% indicates low, moderate, and considerable heterogeneity, respectively.[27] A Cochran Q test of $P < .1000$ was considered significant for heterogeneity. All analyses were conducted in random effects regardless of heterogeneity, as recent evidence has revealed that random effects yield more robust estimates in comparison to fixed effects models.[28] The assessment of publication bias was tested with asymmetry of funnel plot.[29]

Results

Summary of Included Articles

A systematic search of the literature yielded a total of 954 articles. After removal of duplicates, 595 articles were screened, of which 116 articles were selected for full-text review. A total of 22 articles were included in this meta-analysis (Figure 1). Fourteen articles originated from Asia,[16,17,30–41] 4 from Europe,[42–45] 3 from North America,[18,46,47] and 1 from South America.[48] Of 379,801 patients, 116,806 patients were diagnosed with MAFLD, whereas of 67,742 patients, 23,865 met the criteria for NAFLD. For diagnostic modality, 19 studies used imaging, whereas 3 studies used biopsy. All included articles were observational studies. Based on the JBI quality assessment tool, 16 studies were of good quality, whereas 6 studies were of moderate quality. A summary of the included articles and quality assessment can be found in Supplementary Table 1.

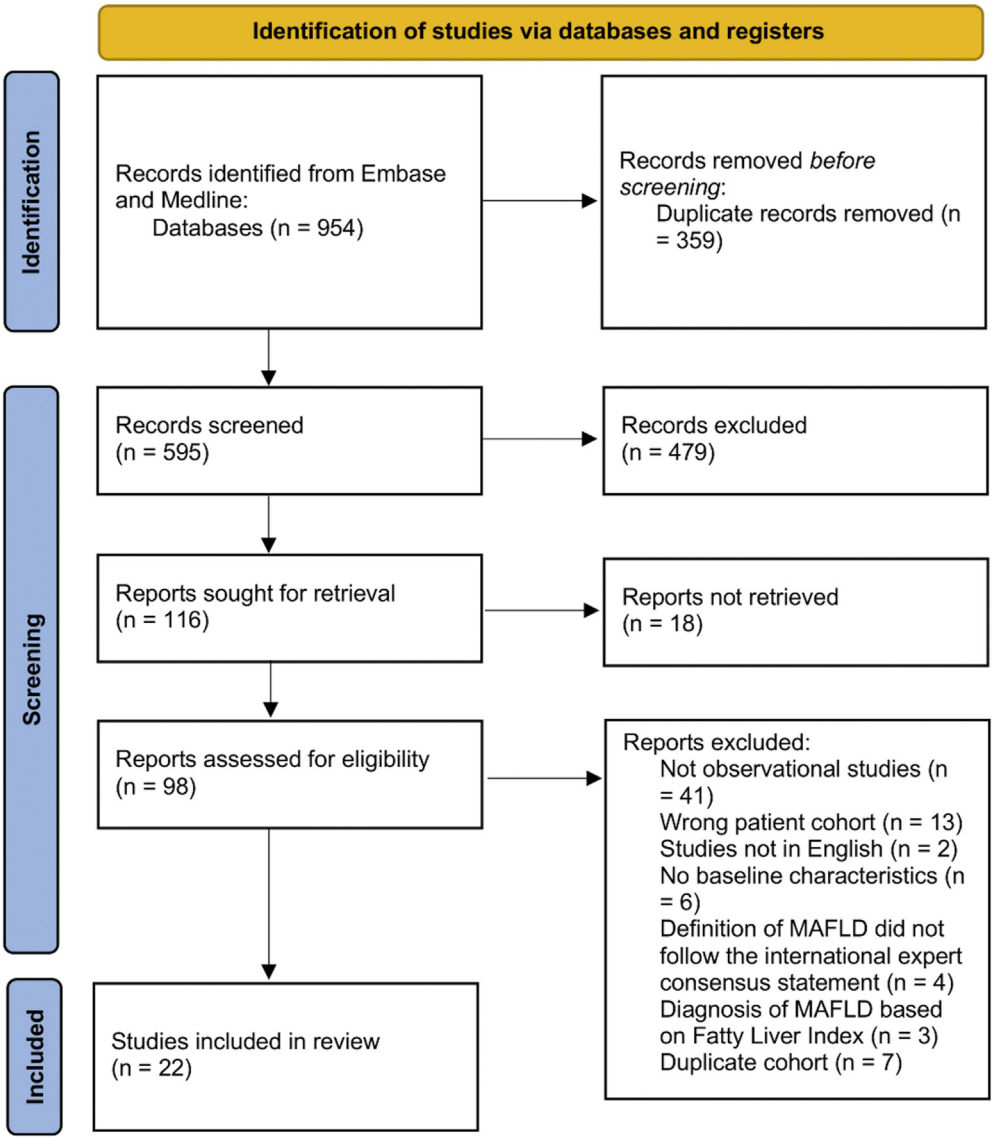

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram.

Prevalence and Characteristics of MAFLD

Overall Prevalence. In the pooled analysis of 22 articles involving 379,801 patients, the overall prevalence of patients diagnosed with MAFLD was 39.22% (95% CI, 30.96%–48.15%). Subgroup analysis of MAFLD prevalence was conducted based on geographical regions (Figure 2). Europe had the highest pooled prevalence of MAFLD at 54.53% (95% CI, 34.76%–72.98%; n = 12,070), followed by Asia (39.89%; 95% CI, 30.26%–50.37%; n = 330,378), and North America (29.08%; 95% CI, 22.17%–37.12%; n = 36,120). In the pooled analysis of 19 studies involving 376,571 patients, the prevalence of MAFLD in patients diagnosed using imaging modality was 42.55% (95% CI, 33.76%–51.85%). Comparatively, the pooled prevalence of MAFLD in patients diagnosed using biopsy modality was 21.19% (95% CI, 12.65%–33.30%; n = 3230). A summary of the results can be found in Table 1.

Characteristics of MAFLD. In total, 21 articles reported baseline characteristics of 25,779 patients with MAFLD (Table 2). The average age of patients with MAFLD was 54.49 years (95% CI, 51.73–57.40 years), with a BMI of 27.76 kg/m^2 (95% CI, 26.24–29.37 kg/m^2). For metabolic parameters, the mean HbA1c was 5.86% (95% CI, 5.80%–5.92%), TG was 1.72 mmol/L (95% CI, 1.61–1.83 mmol/L), HDL was 1.27 mmol/L (95% CI, 1.20–1.34 mmol/L), and LDL was 3.09 mmol/L (95% CI, 2.81–3.39 mmol/L). The pooled estimated glomerular filtration rate was 88.08 mL/min/1.73m^2 (95% CI, 78.98–98.23 mL/min/1.73m^2). For biochemical parameters, liver function test revealed average AST levels to be 28.25 U/L (95% CI, 26.87–29.71 U/L) and ALT levels to be 34.03 U/L (95% CI, 31.23–37.08 U/L). For comorbidities, hypertension had the highest pooled prevalence of 50.71% (95% CI, 43.71%–57.69%), followed by hyperlipidemia (46.92%; 95% CI, 33.76%–60.30%), diabetes (24.66%; 95% CI, 20.76%–28.78%) and lastly, chronic kidney disease (23.92%; 95% CI, 14.13%–35.35%).

Prevalence of MAFLD vs NAFLD

Patients had significantly higher odds of being diagnosed with MAFLD than NAFLD (OR, 1.37; 95% CI, 1.16–1.63; $P < .0010$) (Table 1). There was no publication bias observed in the funnel plot (Supplementary Figure 1). When subgroup analysis was conducted by diagnostic modality, imaging resulted in a significantly higher odds of being diagnosed with MAFLD compared with NAFLD (OR, 1.42; 95% CI, 1.18–1.69; $P < .0010$). However, there was no statistical difference between MALFD and NAFLD with biopsy diagnosis (OR, 1.20; 95% CI, 0.53–2.71; $P = .6590$). Subgroup analysis by region found an increased odds of MAFLD diagnosis compared with NAFLD in Europe and Asia, although there was no statistical difference in North America (Table 1).

Overlap between MAFLD and NAFLD

Among 9006 patients with MAFLD, the pooled prevalence of patients who met the criteria of both MAFLD and NAFLD was 81.59% (95% CI, 66.51%–90.82%) (Figure 2).

Risk Factors Between MAFLD vs NAFLD

There was no significant difference in age (MD, 0.06; 95% CI, −0.48 to 0.59; $P = .8370$) between patients with MAFLD and NAFLD (Table 3). However, patients with MAFLD were more likely to be male (OR, 1.24; 95% CI, 1.10–1.39; $P < .0010$) and have a higher BMI (MD, 0.46 kg/m^2; 95% CI, 0.12–0.80 kg/m^2; $P = .0078$). Patients with MAFLD were also more likely to have hypertension (OR, 1.17; 95% CI, 1.07–1.29; $P = .0007$) (Figure 3) and diabetes (OR, 1.09; 95% CI, 1.00–1.19; $P = .0420$) but not hyperlipidemia (OR, 1.39; 95% CI, 0.54–3.55; $P = .4930$). No significant difference was observed in HbA1c between both groups (MD, 0.02; 95% CI, 0.00–0.04;

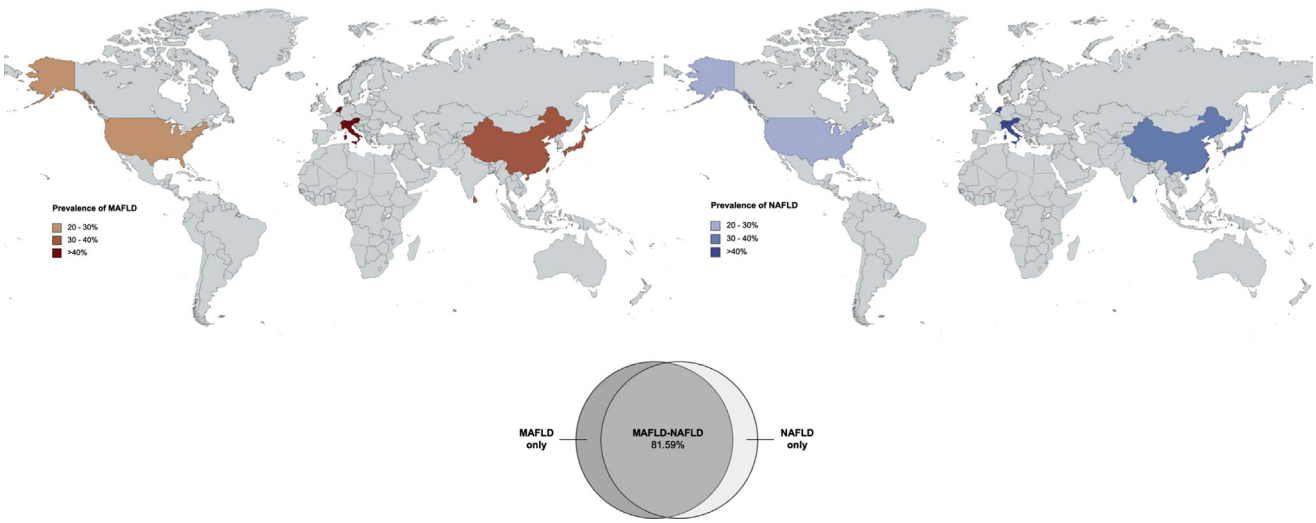

Figure 2. Prevalence by geographical region and overlap between MAFLD and NAFLD.

Table 1. Prevalence of MAFLD and NAFLD

	MAFLD			NAFLD						
	Sample size	Prevalence, %	95% CI	Sample size	Prevalence, %	95% CI	OR	95% CI	*P*-value	I^2	Cochran Q
Overall	379,801	39.22	30.96–48.15	67,743	33.86	23.36–46.22	1.37	1.16–1.63	**< .0010**[a]	97.50%	< .001
Diagnosis type											
Imaging	376,571	42.55	33.76–51.85	64,513	38.28	26.79–51.25	1.42	1.18–1.69	**< .0010**[a]	97.60%	< .001
Biopsy	3230	21.19	12.65–33.30	3,230	18.19	6.57–41.31	1.20	0.53–2.71	.6590	97.30%	< .001
Region											
North America	36,120	29.08	22.17–37.12	36,120	28.48	21.33–36.90	1.03	0.88–1.18	.7100	94.20%	< .001
Europe	12,070	54.53	34.76–72.98	12,070	38.22	13.79–70.53	1.92	1.04–3.53	**.0370**[a]	99.00%	< .001
Asia	330,378	39.89	30.26–50.37	18,320	38.67	25.23–54.09	1.30	1.02–1.67	**.0360**[a]	96.10%	< .001

CI, Confidence interval; MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio.
[a]*P*-value < .05 (boldface) denotes statistical significance.

$P = .0812$). In the assessment of lipids, patients with MAFLD had significantly lower HDL levels (MD, −0.02 mmol/L; 95% CI, −0.04 to 0.00 mmol/L; $P = .0290$) and significantly higher TG (MD, 0.09 mmol/L; 95% CI, 0.04–0.14; $P < .0010$) but not LDL (MD, 0.01 mmol/L; 95% CI, −0.04 to 0.06 mmol/L; $P = .6935$), compared with those with NAFLD.

Liver Enzymes and Fibrosis Scores

There were also statistical differences in liver enzymes (AST and ALT) between patients with MAFLD and NAFLD (MD, 0.89 U/L; 95% CI, 0.35–1.44 U/L; $P = .0014$ and MD, 1.32 U/L; 95% CI, 0.58–2.07 U/L; $P = .0005$, respectively). Assessment of blood fibrosis scores also revealed statistically significant differences in NFS (MD, 0.17; 95% CI, 0.10–0.25; $P < .0001$) and Fibrosis-4 score (MD, 0.04; 95% CI, 0.03–0.06; $P < .0001$) between patients with MAFLD and NAFLD.

Discussion

This meta-analysis seeks to examine the current evidence comparing the prevalence and risk factors of MAFLD and NAFLD in observational studies. With the rise of global obesity,[49] the global prevalence of fatty liver disease is expected to rise exponentially.[50] Yet, proposal for a name change and Definition could have severe implications on our current knowledge of NAFLD. Clinical trials are currently conducted based on the pathogenesis of NAFLD, and a change in definition can hamper progress in clinical trials.[15] Additionally, the change of disease nomenclature can not only profoundly impact patients but also affect health care professionals by potentially creating unnecessary clinical confusion among other providers including cardiologists, diabetologists, and primary care providers who are involved in the care of patients with NAFLD. Presently, the major criticism of the current MAFLD definition lies in the lack of consensus on the definition of "metabolic health,"[15] and concerns have been raised about the utility of nomenclature change.[51] Although NAFLD has a focus on the liver, MAFLD relies heavily on associated comorbidities. The switch of nomenclature would increase focus on these comorbidities but will disadvantage those without clear-cut clinical metabolic risk factors but with NAFLD. The results from this meta-analysis show evident differences in the natural history of NAFLD and NAFLD, with differences in the prevalence, baseline characteristics, and severity scores of patients with MAFLD as compared with NAFLD.

Based on articles using the current Definition proposed by Eslam et al in our meta-analysis,[11] the global prevalence of MAFLD was estimated to be 39.22%, with a higher prevalence recorded in Europe. Blood-based diagnoses of fatty liver (eg, NFS) were

Table 2. Baseline Characteristics of Patients With MAFLD

Characteristics	Total sample size	Effect size	95% CI	I^2	Cochran Q
Age	113,594	54.49	51.73–57.40	99.90%	< .001
BMI, *kg/m²*	62,266	27.76	26.24–29.37	100.00%	< .001
HbA1c,%	13,697	5.86	5.80–5.92	98.50%	< .001
TG, *mmol/L*	102,015	1.72	1.61–1.83	99.80%	< .001
HDL, *mmol/L*	101,143	1.27	1.20–1.34	99.80%	< .001
LDL, mmol/L	100,030	3.09	2.81–3.39	100.00%	< .001
eGFR, *mL/min/1.73m²*	14,112	88.08	78.98–98.23	99.80%	< .001
AST, *U/L*	53,002	28.25	26.87–29.71	99.40%	< .001
ALT, *U/L*	53,002	34.03	31.23–37.08	99.70%	< .001
Hypertension	76,835	50.71	43.71–57.69	99.60%	< .001
Hyperlipidemia	48,054	46.92	33.76–60.30	99.80%	< .001
Diabetes	77,287	24.66	20.76–28.78	99.00%	< .001
CKD	10,925	23.92	14.13–35.35	99.40%	< .001

ALT, Alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic associated fatty liver disease; TG, triglycerides.

Table 3. Risk Factors of MAFLD vs NAFLD

	Total sample size						
Risk factors	MAFLD	NAFLD	Effect Size	95% CI	*P*-value	I^2	Cochran Q
Age, *y*	20,378	18,832	0.06	−0.48 to 0.59	.8400	81.60%	< .001
Gender, *male*	20,378	18,832	1.24	1.10–1.39	**< .0010**[a]	80.30%	< .001
BMI, *kg/m²*	19,234	17,783	0.46	0.12–0.80	**.0078**[a]	92.70%	< .001
Hypertension	19,925	18,756	1.17	1.07–1.29	**.0007**[a]	66.90%	< .001
Diabetes	20,377	18,829	1.09	1.00–1.19	**.0420**[a]	49.20%	.016
Hyperlipidemia	10,116	9604	1.39	0.54–3.55	.4900	98.70%	< .001
Hba1c, %	8542	8046	0.02	0.00–0.04	.0810	57.80%	.020
HDL, *mmol/L*	10,116	9604	-0.02	−0.04 to 0.00	**.0290**[a]	66.40%	.002
TG, *mmol/L*	10,988	10,363	0.09	0.04 to 0.14	**< .0010**[a]	83.30%	< .001
LDL, *mmol/L*	9003	8718	0.01	−0.04 to 0.06	.6900	54.10%	.033
AST, *U/L*	12,257	11,234	0.89	0.35 - 1.44	**.0014**[a]	79.30%	< .001
ALT, *U/L*	12,257	11,234	1.32	0.58–2.07	**.0005**[a]	74.00%	< .001
NFS	7607	7229	0.17	0.10–0.25	**< .0001**[a]	46.80%	.110
Fibrosis-4 score	7827	7372	0.04	0.03–0.06	**< .0001**[a]	0.00%	.810
eGFR, *mL/min/1.73m²*	13,819	13,798	−0.75	−1.55 to 0.05	.0660	48.10%	.100

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAFLD, metabolic associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; TG, triglycerides.
[a]*P*-value < .0500 (boldface) denotes statistical significance.

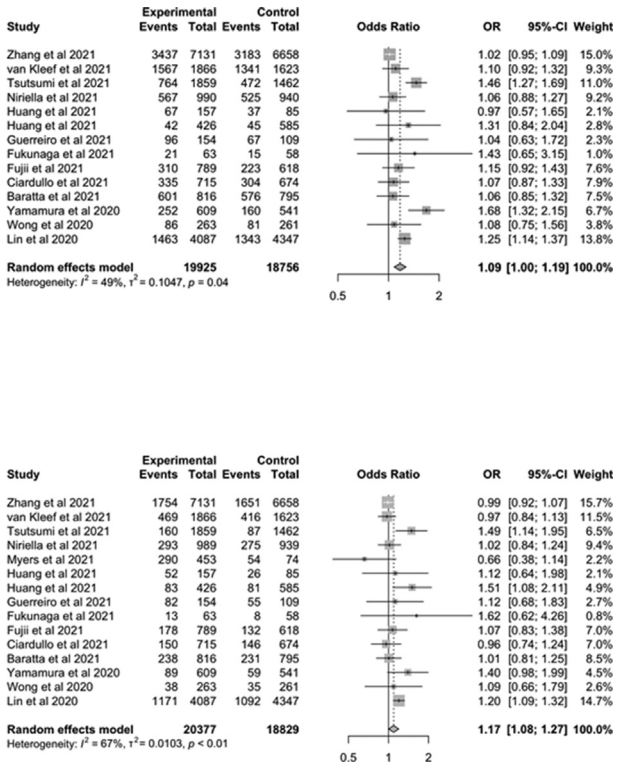

Figure 3. Forest plot of odds ratio for hypertension.

excluded due to poor sensitivity.[52] The higher prevalence is hypothesized to be driven by the characterization of patients with concomitant liver disease, which would be excluded in the previous definition. With MAFLD, patients with obesity, metabolic syndrome, presence of type 2 diabetes mellitus, or any evidence of metabolic dysregulation can be included, whereas the traditional definition of NAFLD focuses primarily on the exclusion of competing etiologies of liver steatosis. In the West, the high disease burden of alcoholic liver disease, which often presents with metabolic abnormalities,[53] can fall under the umbrella of MAFLD and likely accounted for the higher prevalence.[54] Similarly, hepatitis B, which is endemic in certain parts of Asia, can be included under the new definition of MAFLD with the presence of obesity and metabolic dysfunction, which would have otherwise been excluded in NAFLD.[42] Interestingly, there were no significant differences between the rate of biopsy-proven MAFLD and NAFLD. We hypothesized that the lack of difference could be the result of selection bias from the possibility that patients at higher risk of having advanced NAFLD would undergo biopsy and these patients are likely to present with more metabolic risk factors.

Also, gender differences exist between MAFLD and NAFLD, with MAFLD more commonly diagnosed in males. However, NAFLD remains the leading cause of transplant in women due to variations in hormonal state.[9,55] Patients with MAFLD are likely to have a higher prevalence of cardiovascular risk factors including hypertension, hyperlipidemia, and diabetes when compared with patients with NAFLD, who are generally identified to be "healthier."[18,40] MAFLD was also associated with increased levels of transaminitis and fibrosis scores compared with NALFD. A concomitant liver pathology (eg, NAFLD with hepatitis B) included under the MAFLD Definition would inevitably increase the level of fibrosis and inflammation present in the liver, and the degree of fibrosis is a known risk factor for mortality.[56] Although comparison of outcomes were not possible in the present meta-analysis due to the lack of sufficient data, the analysis of adverse events of MAFLD vs NAFLD presents an important gap in literature that warrants further investigations.

Additionally, we found that the current Definition of MAFLD only accounts for 81.59% of patients with NAFLD. Wong et al found that up to 25.0% of patients with incidental fatty liver were not characterized as MAFLD, presumably from the lower metabolic burden despite an increase in fatty liver, and these discrepancies highlight the potential misclassification with the MALFD definition.[17] Although the presence of obesity is highly associated with fatty liver,[57] there remains a subgroup of lean patients with NAFLD who can potentially be misclassified with MAFLD. Lean NAFLD accounts for 19.20% of NAFLD diagnoses,[10] and these patients are less likely to present with metabolic dysregulation. A population study involving 2492 individuals by Younossi et al found that only 6.72% and 17.80% of lean patients with NAFLD had diabetes and hypertension, respectively.[58] Similar results by Kumar et al showed that only 3.70% and 15.00% of lean patients with NAFLD had diabetes and hypertension, respectively.[59] Patients with NAFLD have also been reported to develop incident metabolic dysfunction only after the development of NAFLD.[60] These patients will not be classified as MAFLD but may truly have disease that has yet to fulfil the definitions of MAFLD.

Limitations

This meta-analysis summarizes the current evidence between NAFLD and MAFLD. However, there are several limitations to this study. Biopsy remains the gold standard for diagnosis of fatty liver, and although it would be ideal to only include biopsy-proven liver steatosis, larger observational studies were conducted with noninvasive diagnosis of NAFLD similar to previous studies.[10] Instead, we opted to perform a subgroup analysis by diagnostic modality to control for heterogeneity. Additionally, heterogeneity measures (I^2) reported in this meta-analysis remain high (I^2 >90%). Similar to previous meta-analyses[10,61] the inclusion of large patient sample sizes can often result in a large I^2. Heterogeneity is an inherent limitation of meta-analyses conducted with observational studies.[62] Also, outcome data comparing between the 2 etiologies remain scarce, with

current comparisons centered around MAFLD vs no MAFLD rather than MAFLD vs NAFLD. Although the evidence is yet to mature, it is likely that the presence of dual pathology will increase the rate of adverse outcomes between MAFLD and NAFLD. Other risk factors, such as homeostatic model assessment for insulin resistance score and C-reactive protein, were not considered for analysis due to the paucity of data in included studies and their limited value in discriminating between the 2 etiologies.

Conclusions

The evidence from this meta-analysis suggests stark differences between NAFLD and MAFLD, with an estimated 20% of patients not captured by the new Definition. Although MAFLD was thought to improve the characterization of the disease, the definition remains to yet be endorsed by the American Association for the Study of Liver Diseases and EASL. The differences in prevalence, risk factors, transaminitis, and fibrosis paints a clear difference between the 2 etiologies and would preclude an interchangeable reference for fatty liver. However, if clinicians adopt the use of MAFLD, a greater emphasis should be placed on collaborative care models for patients with an increased metabolic burden.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.11.038.

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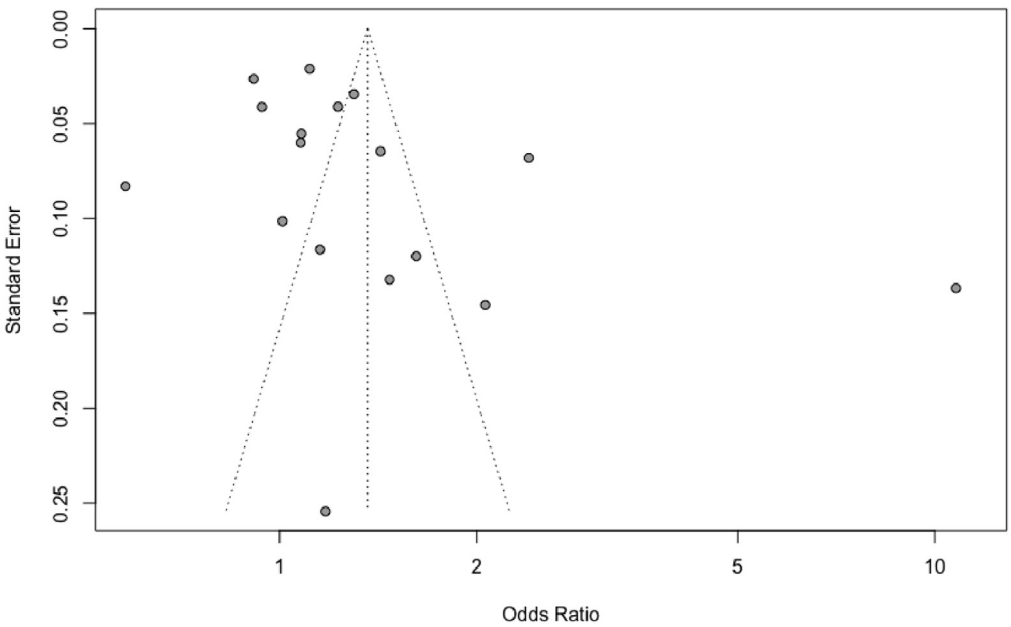
Conflicts of interest

The authors disclose the following: Arun J. Sanyal is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect; and Galmed; has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Jannsen, Gilead, Terns, Birdrock, Merck, Valeant, Boehringer-Ingelheim, Lilly, Hemoshear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exhalenz, and Genfit; has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Zydus, Nordic Bioscience, Albireo, Prosciento, Surrozen, and Bristol Myers Squibb; and receives royalties from Elsevier and UptoDate; his institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, Astra Zeneca, Malinckrodt, Cumberland, and Norvatis. Mazen Noureddin has been on the advisory board for 89BIO, Gilead, Intercept, Pfizer, Novo Nordisk, Blade, EchoSens, Fractyl, Terns, Siemens, and Roche diagnostic; has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking, and Zydus; and is a minor shareholder or has stocks in Anaetos, Rivus Pharma, and Viking. The remaining authors disclose no conflicts.

Joanna Briggs Institute Critical Appraisal Checklist

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measures similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?



Supplementary Figure 1. Funnel plot for prevalence of MAFLD vs NAFLD

Supplementary Table 1. Summary of Included Articles

Author	Year of publication	Region	Diagnosis type	Prevalence of MAFLD/ NAFLD			Mean age, *y*		Gender (male)		Quality Assessment
				Sample size	Events (MAFLD)	Events (NAFLD)	MAFLD	NAFLD	MAFLD	NAFLD	
Zhang et al	2021	North America	Imaging	19,617	7131	6658	50.80	50.90	4169	3801	9
Wang et al	2021	Asia	Imaging	152,139	47,995	–	50.21	–	40318	–	9
Van Kleef et al	2021	Europe	Imaging	5445	1866	1623	69.74	69.95	807	675	10
Tsutsumi et al	2021	Asia	Imaging	2306	1859	1462	51.00	51.00	1350	879	9
Semmler et al	2021	Europe	Imaging	4718	2189	2262	60.40	–	1396	–	10
Niriella et al	2021	Asia	Imaging	2985	990	940	53.33	53.33	380	323	11
Myers et al	2021	Europe	Imaging	920	453	76	68.34	75.00	375	52	11
Liu et al	2021	Asia	Imaging	6232	2287	–	57.52	–	804	–	11
Huang et al	2021	Asia	Biopsy	780	157	85	51.61	50.50	87	42	9
Huang et al	2021	Asia	Biopsy	1217	426	585	40.39	39.41	361	489	11
Guerreiro et al	2021	South America	Biopsy	1233	154	109	57.00	54.67	74	45	10
Fukunaga et al	2021	Asia	Imaging	124	63	58	58.67	57.00	52	48	11
Fujii et al	2021	Asia	Imaging	2254	789	618	54.00	54.00	586	423	11
Fan et al	2021	Asia	Imaging	5377	1571	–	67.00	–	555	–	11
Ciardullo et al	2021	North America	Imaging	3420	715	674	51.17	51.25	398	371	10
Chen et al	2021	Asia	Imaging	139,170	36,306	–	47.00	–	27684	–	11
Baratta et al	2021	Europe	Imaging	987	816	795	56.00	55.80	501	484	9
Yamamura et al	2020	Asia	Imaging	765	609	541	56.00	55.00	308	183	10
Wong et al	2020	Asia	Imaging	1016	263	261	51.00	51.00	139	140	11
Li et al	2020	Asia	Imaging	9140	2868	–	53.70	–	1144	–	10
Lin et al	2020	North America	Imaging	13,083	4087	4347	48.39	46.81	2036	2014	10
Liang et al	2021	Asia	Imaging	6873	19,617	2771	–	–	–	–	8

MAFLD, Metabolic associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease.

Supplementary Appendix 1. PRISMA 2020 for Abstracts Checklist

Section and topic	Item #	Checklist item	Reported (Yes/No)
Title			
Title	1	Identify the report as a systematic review.	Yes
Background			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
Methods			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (eg, databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
Results			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (ie, which group is favoured).	Yes
Discussion			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (eg, study risk of bias, inconsistency, and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
Other			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Supplementary Material 2. PRISMA 2020 Checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	9
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	5
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	7-8
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	9
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	9
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Supplementary Material 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	9 – 10
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9 - 10
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9 - 10

Continued

Section and topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	10 - 11
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	11
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9 – 10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression).	11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	10-11
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	11
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Supplementary Material 4

Continued

Section and topic	Item #	Checklist item	Location where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Material 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	Supplementary Material 3
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	12 – 15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary Material 4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplementary Material 4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	12 - 14
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	15-16
	23b	Discuss any limitations of the evidence included in the review.	17
	23c	Discuss any limitations of the review processes used.	17
	23d	Discuss implications of the results for practice, policy, and future research.	17
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	9
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	9
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-

Continued

Section and topic	Item #	Checklist item	Location where item is reported
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	3
Competing interests	26	Declare any competing interests of review authors.	3
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	3

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.