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Nonalcoholic fatty liver disease and health outcomes: An umbrella review of systematic reviews and meta-analyses

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Abstract

Purpose: A large number of systemic reviews and meta-analyses have explored the relationship between nonalcoholic fatty liver disease (NAFLD) and multiple health outcomes. The aim of this study is to conduct an umbrella review to assess the strength and evidence for the association between NAFLD and health outcomes.

Methods: We systematically identified the present meta-analyses of observational studies reporting an association between NAFLD and health outcomes. For each meta-analysis, we assessed the quality with AMSTAR2 and graded the epidemiologic evidence.

Results: Fifty-four articles comprising 111 unique meta-analyses were included in this study. Eighty-five unique outcomes showed significant associations ($P \leftarrow 0.05$), whereas 26 unique outcomes showed insignificant associations, and we cannot assess the epidemiologic evidence. For 85 significant health outcomes, four outcomes (carotid intima-media thickness (C-IMT), peak A velocity, left ventricle end-diastolic diameter, incident chronic kidney disease (CKD) in adult patients) was graded as high quality of evidence, 23 outcomes were graded as the moderate quality of evidence, and the remaining 58 outcomes were graded as weak quality of evidence. Fourty-seven (87.03%) studies showed critically low methodological quality.

Conclusion: In this umbrella review, only four statistically significant health outcomes showed high epidemiologic evidence. NAFLD seems to relate to an increased risk of C-IMT, peak A velocity, left ventricle end-diastolic diameter, and incident CKD in adult patients.

Keywords: health outcomes, meta-analysis, nonalcoholic fatty liver disease, umbrella reviews

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Introduction

The global prevalence of nonalcoholic fatty liver disease (NAFLD) has only been increasing in the population and suspect to increase in the future leading to increase global burden. NAFLD affects up to 25% of adults, up to 3~10% of the Western pediatric population and increases up to 70% among obese children.[1] Many research studies have demonstrated how NAFLD can contribute to several disease processes including hepatic, extrahepatic diseases, and overall increase in mortality.[2,3] It is becoming the most common and major cause of chronic liver disease worldwide, especially in high-income countries, resulting in considerable liver-related disease such as hepatocellular carcinoma (HCC),[4] cryptogenic liver cirrhosis,[5] and liver-specific mortality.[6] It is also a major cause of extrahepatic disease with earlier studies demonstrating that NAFLD also contributed to the risk of cardiovascular diseases[7,8] and diabetes.[9] The risk factors for cardiovascular diseases and diabetes are also known for metabolic syndrome. According to Lonardo *et al.*,[10] NAFLD is not only a manifestation but also a precursor of the metabolic syndrome. In recent research studies, there has been further investigation regarding NAFLD association with other diseases. A great number of studies and meta-analyses have

demonstrated that NAFLD may increase the risk of various diseases, including gastrointestinal diseases,[11–13] chronic kidney diseases (CKD),[14,15] atrial fibrillation,[16] and all-cause and cause-specific mortality,[17] indicating that NAFLD poses a threat to human health.

Although multiple investigations explored the correlation between NAFLD and other health outcomes, the reported associations may be flawed. The magnitudes of the observed effects are affected by inherent biases such as selective bias, publication bias, and residual confounding.[18,19] Despite many systematic reviews and meta-analyses that have examined NAFLD and other health outcomes, to our knowledge, there have been no systematic efforts to accurately summarize and critically appraise the evidence. Umbrella review is increasingly more important for overviewing the evidence of systematic and meta-analyses on a specific topic. An umbrella review focused on a specific disease that can provide important guidance and reliable evidence for prevention, diagnosis, and treatment. We performed an umbrella review of observational meta-analyses to comprehensively assess methodological quality, investigate potential bias, and evaluate the epidemiologic evidence of the associations between NAFLD and health information. We believe that this work can provide useful information about NAFLD and human health.

Materials and methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocols to research literature systematically.[20] Before beginning the umbrella review, we registered the protocol with PROSPERO (registration number: CRD42021279078).

Literature search

PubMed, Web of Science, and Cochrane Database of Systematic Reviews were searched from the initiation to September 2021. The search terms applied were ('Meta-Analysis' OR 'metaanaly' OR 'meta-analy' OR 'Systematic review' OR 'systematic review' AND 'Nonalcoholic Fatty Liver Disease' OR 'NAFLD' OR 'Nonalcoholic Fatty Liver Disease' OR 'Fatty Liver, Nonalcoholic' OR 'Fatty Livers, Nonalcoholic' OR 'Liver, Nonalcoholic Fatty' OR 'Livers, Nonalcoholic Fatty' OR 'Nonalcoholic Fatty Live' OR 'Nonalcoholic Fatty Livers' OR 'Nonalcoholic Steatohepatitis' OR 'Nonalcoholic Steatohepatitides' OR 'Steatohepatitides, Nonalcoholic' OR 'Steatohepatitis, Nonalcoholic'). We also manually screened the reference to identify the eligible articles. LZ and WC independently conducted the literature search. Any discrepancies were discussed and resolved with ST.

Selection criteria

Two authors (LZ and CW) scrutinized independently the full texts of potentially eligible articles. Only the meta-analyses of the epidemiological studies examining the relationship between NAFLD and other health outcomes in humans were considered. Trials and meta-analyses of interventional trials were not available for our study. The protocols, abstracts of the conference, and letters to editors were also excluded. When several meta-analyses simultaneously reported the same health outcome, we included the one with the largest number of studies.

Data extraction

The data of included studies were extracted by two authors separately. For each eligible meta-analysis, we extracted the following information: the first author, publication year, the design of studies, the number of participants and cases, the effects sizes (SMD, WMD, MD, ORs, RRs, or HRs), the p values of pooled effects, Cochrane Q measurement, Egger 's test measurement and I^2. When we met discrepancies, we resolved them through discussion.

Assessment of methodological quality

Two authors used AMSTAR 2,[21] which consists of 16 items, to assess the methodologic quality of each included meta-analysis independently. AMSTAR 2 is a strict and reliable measurement tool to evaluate the quality of systematic reviews and meta-analyses. According to the AMSTAR 2 scores, four grades (high, moderate, low, and critically low) were categorized to describe the result of methodologic quality. No or only one non-critical defect is considered high methodologic quality and more than one non-critical defect is considered moderate methodologic quality. Only one critical weakness with or without non-critical defects is considered low method quality and

more than one critical weakness with or without critical defects is considered critically low methodologic quality. Discrepancies between AMSTAR 2 scores were resolved by discussion.

Evaluation of the evidence quality

We classified the evidence from meta-analyses of observational studies with the parameters that have been applied in various fields.[22–26] The parameters consist of the following criteria: (1) precision of the estimate (p value for the estimate < 0.001[27,28] and the number of cases $\geqslant 1000$; (2) no heterogeneity ($I^2 < 50\%$ and p value for Cochran Q-test > 0.10); (3) no evidence of small-study effects (p value for Egger's test > 0.10). The strength of epidemiologic evidence was categorized into high (if all these criteria were satisfied), moderate (if p value for estimate < 0.001 with a maximum of 1 criterion was not satisfied), or weak (p value for estimate < 0.05 with all other cases). If the p value for estimate > 0.05, the evaluation of evidence quality was not applicable.

Data analysis

According to the extracted raw data from each published study, we recalculated the missing data (*ig*. heterogeneity and publication bias) with a random-effects model whenever possible. When the p value was<0.05, the total impacts of pooled meta-analyses were considered significant. I^2 test and Q test were used to evaluate the heterogeneity between studies and publication bias was calculated by Egger's test. The p value < 0.1 for heterogeneity and publication bias were both considered significant.

Results

Characteristics of the meta-analyses

The results of systematic research and selection of eligible meta-analyses are summarized in Figure 1. Overall, a total of 2200 research articles were investigated from PubMed ($n = 1295$), Web of Science ($n = 862$), and Cochrane database ($n = 43$). After excluding the 17 articles and 53 overlapping meta-analyses (Supplementary Table 1), 54 articles with 111 unique health outcomes were included[29–82] (Table 1). The publication dates of these studies range from 2013 through 2021. Among the meta-analyses included in our umbrella review, the median number of primary studies was 7 (range: 2–30), the medium number of participants was 19,274 (range: 146–613,715) and the median number of cases was 1444 (range: 44–36,448). As we see in Figure 2, health outcomes associated with NAFLD relate to the following categories of diseases: cardiovascular disorders ($n = 36$), cerebral and cerebrovascular disease ($n = 5$), skeletal system disorders ($n = 9$), mortality ($n = 8$), metabolic disorders ($n = 3$), digestive disorders ($n = 20$), nephrological disorders ($n = 3$), urological disorders ($n = 2$), serum marker disorders ($n = 10$), respiratory system disorders ($n = 3$), and other health outcomes ($n = 12$) (Figure 2). Among 111 unique meta-analyses, 85 (76.58%) reported significant summary outcomes ($p < 0.05$) and the remaining 26 (23.42%) meta-analyses showed no significant association with NAFLD. According to the statistically significant outcomes, it can be concluded that NAFLD may increase the risk of a wide variety of diseases and have harmful effects on human health.

Heterogeneity

According to Table 1, we recalculated the two results of two articles[34,44] because they did not report the outcomes of heterogeneity. However, owing to the lack of raw data in one article,[46] we failed to recalculate the I^2 and the p value for the Cochran Q-test by random or fixed model, so the heterogeneity was not able to be evaluated. Among the 111 unique meta-analyses, only 26 (23.42%) health outcomes indicated no heterogeneity ($I^2 < 50\%$ and p value for Cochran Q-test $\geqslant 0.1$), whereas 85 (76.58%) health outcomes showed significant heterogeneity ($I^2 \geqslant 50\%$ and p value for Cochran Q-test < 0.1).

Publication bias

Fifty-three outcomes were recalculated using the Egger's test through which the raw data in each included meta-analysis to evaluate for potential publication bias. Due to the small number of studies, there were still 21 outcomes in 15 articles that could not be recalculated using the Egger's test,[32,40,49,57–59,61,65,67,70–72,74,76,79] thus we were not able to assess their publication bias. In the end, 71 health outcomes had no publication bias (p value for Egger's test $\geqslant 0.1$) while 19 health outcomes presented publication bias (p value for Egger's test < 0.1).

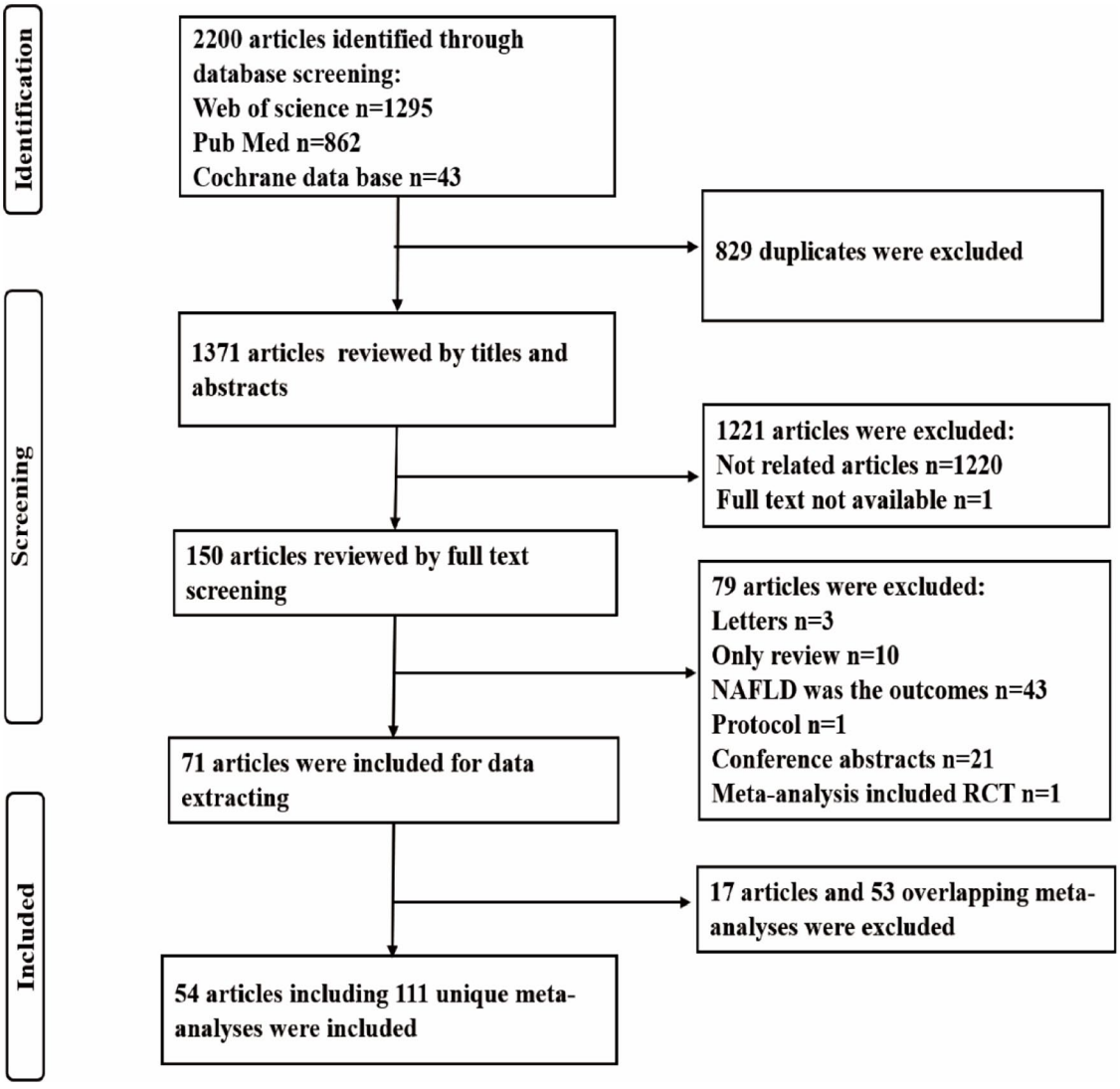

Figure 1. The PRISMA consort flow diagram of literature search and study selection.

Methodological Quality Assessment

The 16 items including in AMSTAR 2 and the result of the methodological qualities assessment of the 54 included articles are presented in Table 2. Only 7 (12.96%) articles were assessed to be low methodological quality, and the remaining 47 (87.04%) articles were assessed to be critically low (Figure 3). It is worthy to note that there were no high/moderate methodological quality based on the AMSTAR 2 criteria. The major critical flaws were the absence of registered protocol ($n = 40$, 75.47%), the inadequacy of the literature search ($n = 52$, 96.30%) and without the list for excluding primary studies ($n = 39$, 72.22%).

Strength of epidemiologic evidence

The results of epidemiologic evidence are shown in Table 3. According to the criteria mentioned above, the assessment of epidemiologic evidence was not applicable for 26 (23.42%) health outcomes because their p value for pooled effects were more than 0.05 which was not statistically significant. The relevant criteria were considered to be not satisfied if a meta-analysis lacked the result of heterogeneity and publication bias. Among the remaining 85 statistically significant health outcomes, only 4 (3.60%) outcomes were rated as high epidemiologic evidence, 23 (20.72%) outcomes showed moderate

Table 1. Characteristics of the unique meta-analyses investigating the associations between NAFLD and multiple health outcomes.

Health outcomes	Author	Studies (*n*)	NAFLD diagnosis	Participants (*n*)	Cases (*n*)	Type of metric	Effect size		Heterogeneity		Small-study effect
							95% CI	*p* value	I^2	*p* value	
Cardiovascular disorders											
C-IMT in adult patients	Madan *et al.*[33]	20 observational studies	Biopsy and US	19,274	8652	SMD	0.94 (0.78, 1.16)	<0.001	0.0	0.754	0.14
Carotid plaque in adult patients	Madan *et al.*[33]	13 observational studies	Biopsy and US	14,445	5399	OR	1.77 (1.21, 2.581)	0.003	0.0	0.561	0.76
C-IMT in pediatric patients	Madan *et al.*[33]	5 observational studies	Biopsy and US	1121	312	SMD	1.08 (0.46, 1.71)	0.001	0.0	0.612	0.46
CAC	Zhou *et al.*[54]	5 cross-sectional studies and 2 cohorts	Biopsy, US, and CT	29,531	12,606	OR	1.40 (1.22, 1.60)	<0.00001	59.0	0.02	0.097*
Arterial stiffness	Zhou *et al.*[54]	4 cross-sectional studies	Biopsy, US, and CT	50,369	10,867	OR	1.56 (1.24, 1.96)	0.0002	65.0	0.03	0.203*
Endothelial dysfunction	Zhou *et al.*[54]	3 cross-sectional studies	Biopsy, US, and CT	426	280	OR	3.73 (0.99, 14.09)	0.05	67.0	0.05	0.019*
Subclinical atherosclerosis	Ampuero *et al.*[31]	4 cross-sectional studies and 6 cohort studies	US	2932	NA	OR	2.42 (1.98, 2.96)	<0.001*	12.5	0.33	0.14
CAC score > 0	Jaruvongvanich *et al.*[37]	12 cross-sectional studies	US and CT	NA	NA	OR	1.41 (1.26, 1.57)	<0.001*	66.0	0.07	<0.01
CAC score > 100	Jaruvongvanich *et al.*[37]	8 cross-sectional studies	US and CT	NA	NA	OR	1.24 (1.02, 1.52)	>0.05*	42.0	0.10	0.62
Fatal CVD	Targher *et al.*[41]	7 cohort studies	Biopsy, US, CT, and liver enzyme	NA	1326	OR	1.31 (0.87, 1.97)	0.202	90.3	0.000	0.475
Fatal and non-fatal CVD	Targher *et al.*[41]	5 cohort studies	Biopsy, US, CT, and liver enzyme	NA	1272	OR	1.63 (1.06, 2.49)	0.025	83.0	0.000	0.274
Non-fatal CVD	Targher *et al.*[41]	5 cohort studies	Biopsy, US, CT, and liver enzyme	NA	385	OR	2.52 (1.52, 4.18)	<0.001*	60.9	0.037	0.642
CAD	Wu *et al.*[42]	9 cross-sectional studies and 9 cohort studies	Biopsy, US, and liver enzyme	20,198	NA	HR	1.82 (1.23, 1.67)	0.002	57.2	0.096	0.248
CVD	Veracruz *et al.*[81]	12 cross-sectional studies, 16 cohort studies, and 2 case–control studies	Biopsy, US, CT, and FLI	192,107	36,448	RR	1.78 (1.52, 2.08)	<0.00001	95.0	<0.00001	0.185*
LVEF	Borges-Canha *et al.*[55]	14 cross-sectional studies	Biopsy, US, and CT	25,338	17,583	MD	−0.30 (−0.90, 0.30)	0.33	70.0	<0.00001	0.516*

(Continued)

Table 1. (Continued)

Health outcomes	Author	Studies (*n*)	NAFLD diagnosis	Participants (*n*)	Cases (*n*)	Type of metric	Effect size		Heterogeneity		Small-study effect
							95% CI	*p* value	I^2	*p* value	
Peak E velocity	Borges-Canha *et al.*[55]	8 cross-sectional studies	Biopsy, US, and CT	17,605	15,160	MD	−3.63 (−7.56, 8.98)	0.07	89.0	<0.00001	0.082*
E/e' ratio	Borges-Canha *et al.*[55]	8 cross-sectional studies	Biopsy, US, and CT	22,270	16,523	MD	1.05 (0.61, 1.50)	<0.00001	93.0	<0.00001	0.228*
Peak A velocity	Borges-Canha *et al.*[55]	7 cross-sectional studies	Biopsy, US, and CT	17,542	15,122	MD	3.55 (2.70, 4.39)	<0.00001	4.0	0.4	0.976*
E/A ratio	Borges-Canha *et al.*[55]	12 cross-sectional studies	Biopsy, US, and CT	25,149	17,461	MD	−0.15 (−0.22, −0.88)	<0.00001	94.0	<0.0001	0.845*
Isovolumic relaxation time	Borges-Canha *et al.*[55]	5 cross-sectional studies	Biopsy, US, and CT	311	175	MD	10.00 (4.03, 15.97)	0.001	84.0	<0.0001	0.573*
Deceleration time	Borges-Canha *et al.*[55]	9 cross-sectional studies	Biopsy, US, and CT	23,396	16,583	MD	13.04 (5.37, 20.71)	0.0009	89.0	<0.00001	0.001*
Left ventricle mass	Borges-Canha *et al.*[55]	6 cross-sectional studies	Biopsy, US, and CT	18,785	15,093	MD	47.22 (33.25, 61.18)	<0.00001	92.0	<0.00001	0.055*
Left ventricle end-diastolic diameter	Borges-Canha *et al.*[55]	8 cross-sectional studies	Biopsy, US, and CT	19,482	16,192	MD	1.32 (0.93, 1.70)	<0.00001	38.0	0.13	0.410*
Left ventricle end-systolic diameter	Borges-Canha *et al.*[55]	7 cross-sectional studies	Biopsy, US, and CT	19,419	16,154	MD	−0.31 (−1.28, 0.66)	0.53	93.0	<0.00001	0.402*
Left atrium diameter	Borges-Canha *et al.*[55]	8 cross-sectional studies	Biopsy, US, and CT	20,704	16,334	MD	2.19 (1.04, 3.35)	0.0002	95.0	<0.00001	0.154*
Posterior wall thickness	Borges-Canha *et al.*[55]	7 cross-sectional studies	Biopsy, US, and CT	19,428	16,160	MD	1.14 (0.75, 1.53)	<0.00001	96.0	<0.00001	0.510*
Interventricular septum thickness	Borges-Canha *et al.*[55]	8 cross-sectional studies	Biopsy, US, and CT	19,482	16,192	MD	1.06 (0.67, 1.45)	<0.00001	94.0	<0.00001	0.738*
LV mass indexed to BSA	Bonci *et al.*[32]	4 cross-sectional studies	Biopsy and US	254	160	SMD	0.84 (0.25, 1.41)	<0.0001	78.8	<0.004	NA
LV mass indexed to height	Bonci *et al.*[32]	3 cross-sectional studies	Biopsy and US	736	244	SMD	0.152 (−0.01, 0.32)	0.069	0.0	0.87	NA
EFT thickness	Oikonomidou *et al.*[78]	3 observational studies	Biopsy	347	211	MD	1.17 (0.45, 1.89)	<0.001	89.0	0.001	0.17*
GLS	Oikonomidou *et al.*[78]	3 observational studies	Biopsy	146	67	MD	−3.17 (−5.09, −1.24)	<0.001	89.0	0.0001	0.875*

(Continued)

Table 1. (Continued)

Health outcomes	Author	Studies (*n*)	NAFLD diagnosis	Participants (*n*)	Cases (*n*)	Type of metric	Effect size		Heterogeneity		Small-study effect
							95% CI	*p* value	I^2	*p* value	
Diastolic cardiac dysfunction	Wijarnpreecha *et al.*[51–53]	12 cross-sectional studies	US, CT, and ICD code	280,645	NA	OR	2.02 (1.47, 2.79)	<0.0001	89.0	<0.00001	0.0002
Cardiac conduction defect	Wijarnpreecha *et al.*[71]	3 cross-sectional studies	US, CT, and ICD code	3651	NA	OR	5.17 (1.34, 20.01)	0.02	96.0	<0.0001	NA
Atrial fibrillation	Cai *et al.*[63,64]	6 cohort studies	US, CT, and FLI	613,715	7271	RR	1.19 (1.07, 1.31)	0.001*	54.0	0.05	0.227*
Epicardial adipose tissue	Liu *et al.*[57,58]	13 case–control studies	NR	4540	2260	SMD	0.73 (0.51, 0.94)	<0.001	88.6	0.000	NA
Hypertension and prehypertension	Yao *et al.*[48]	5 observational studies	NR	36,534	NA	OR	1.30 (1.14, 1.47)	0.000	65.6	0.002	0.001
Cerebral and cerebrovascular disease											
Cerebrovascular accident	Hu *et al.*[49]	2 case–control studies and 7 cohort studies	NR	6183	390	OR	2.32 (1.84, 2.93)	<0.001	0.0	0.895	0.578
Ischemic stroke	Hu *et al.*[49]	2 case–control studies and 3 cohort studies	NR	4009	313	OR	2.51 (1.92, 3.28)	<0.001	0.0	0.828	0.001*
Cerebral hemorrhage	Hu *et al.*[49]	2 cohort studies	NR	1980	51	OR	1.85 (1.05, 3.27)	0.034	0.0	0.544	NA
Stroke and cerebrovascular diseases	Veracruz *et al.*[81]	16 cohorts	Biopsy, US, CT, and FLI	34,336	29,314	RR	2.08 (1.72, 2.51)	<0.00001	91.0	<0.00001	0.02*
Stroke	Mahfood Haddad *et al.*[44]	3 cohort studies	NR	2241	NA	RR	2.09 (1.46, 2.98)*	<0.001*	14.8*	0.309*	0.860*
Digestive disorder											
Gallstone disease	Qin and Ding[40]	3 cross-sectional studies and 2 cohort studies	Biopsy and US	42,623	15,377	OR	1.75 (1.51, 2.04)	<0.01	57.0	0.05	NA
Cholangiocarcinoma	Wongjarupong *et al.*[47]	7 cross-sectional studies	NR	138,213	1444	OR	1.95 (1.36, 2.79)	0.000	76.0	<0.01	0.82
HCC with/without cirrhosis	Stine *et al.*[50]	12 observational studies	Biopsy and US	145,512	20,900	OR	1.43 (0.77, 2.65)	0.25	99.0	<0.00001	0.625*
HCC without cirrhosis	Stine *et al.*[50]	2 cross-sectional studies and 5 cohort studies	Biopsy and US	23,059	3567	OR	2.61 (1.27, 5.35)	0.009	95.0	<0.00001	0.671*

(Continued)

Table 1. (Continued)

Health outcomes	Author	Studies (*n*)	NAFLD diagnosis	Participants (*n*)	Cases (*n*)	Type of metric	Effect size		Heterogeneity		Small-study effect
							95% CI	*p* value	I^2	*p* value	
ICC	Liu *et al.*[69]	6 case–control studies	Biopsy, US, CT, and ICD code	466,101	NA	OR	2.46 (1.77, 3.44)	0.000*	72.6	0.003	0.640*
ECC	Liu *et al.*[69]	5 case–control studies	Biopsy, US, CT, and ICD code	458,582	NA	OR	2.24 (1.58, 3.17)	0.000*	68.4	0.023	0.447*
Colorectal adenoma	Chen *et al.*[56]	8 cross-sectional studies and 4 cohort studies	Biopsy and US	22,482	NA	OR	1.49 (−1.20, 1.84)	0.000*	83.5	<0.001	0.945
Colorectal cancer	Liu *et al.*[69]	5 cross-sectional studies and 5 cohort studies	Biopsy, US, CT, and ICD code	NA	NA	OR	1.72 (1.40, 2.11)	0.000*	83.4	0.000	0.001*
Recurrent colorectal adenoma/cancer	Chen *et al.*[56]	4 cohort studies	Biopsy and US	2201	NA	OR	1.73 (1.12, 2.68)	0.014*	47.2	0.128	0.734
Right colon tumors	Lin *et al.*[75]	4 cross-sectional studies and 5 cohort studies	Biopsy, US, and CT	7895	1012	OR	1.65 (1.44, 1.89)	<0.00001	58.0	0.02	0.567*
Left colon tumors	Lin *et al.*[75]	4 cross-sectional studies and 5 cohort studies	Biopsy, US, and CT	8675	1276	OR	1.41 (1.24, 1.61)	<0.00001	59.0	0.02	0.601*
Esophagus cancer	Mantovani *et al.*[76,77]	5 cohort studies	US and ICD code	140,014	125	HR	1.93 (1.19, 3.12)	0.008*	45.1	0.121	0.264*
Stomach cancer	Mantovani *et al.*[76,77]	6 cohort studies	US and ICD code	155,944	597	HR	1.81 (1.19, 2.75)	0.005*	80.8	0.000	0.0345*
Pancreas cancer	Mantovani *et al.*[76,77]	3 cohort studies	US and ICD code	55,655	115	HR	1.84 (1.23, 2.74)	0.003*	0.0	0.402	0.963*
IP by means of 5-6 h L/M or L/R	De Munck *et al.*[66]	7 observational studies	Biopsy and US	205	119	SMD	0.79 (0.49, 1.08)	<0.00001	0.0	0.43	0.532*
IP by means of serum zonulin	De Munck *et al.*[66]	5 observational studies	Biopsy and US	353	191	SMD	1.04 (0.40, 1.68)	0.0001	86.0	<0.001	0.683*
Gastroesophageal reflux disease	Xue *et al.*[62]	6 cross-sectional studies, 2 cohort studies, and 1 case–control study	US	79478	NA	OR	1.28 (1.12, 1.44)	0.000*	82.0	0.000	<0.001
Overall survival of AP	Váncsa *et al.*[70]	2 cohort studies	NR	1396	44	OR	2,81 (0.38, −20.03)	0.301*	68.7	0.074	NA
Moderately severe/ severe AP	Váncsa *et al.*[70]	3 cohort studies	NR	NA	NA	OR	3.39 (1.51, 7.56)	0.003*	79.2	0.008	0.032*
Colorectal polyps	Chen *et al.*[56]	12 cross-sectional studies, 6 cohort studies, and 2 case–control study	Biopsy and US	142,387	17,967	OR	1.45 (1.22, 1.72)	0.000*	72.4	0.057	NA

(Continued)

Table 1. (Continued)

Health outcomes	Author	Studies (*n*)	NAFLD diagnosis	Participants (*n*)	Cases (*n*)	Type of metric	Effect size		Heterogeneity		Small-study effect
							95% CI	*p* value	I^2	*p* value	
Skeletal system disorders											
Total BMD	Mantovani *et al.*[13]	1 case–control study and 1 cross-sectional study	Biopsy, US, and transient elastography	1994	690	WMD	−0.04 (−0.16, 0.08)	**>0.05**	98.9	0.000	NA
BMD at the lumbar spine	Mantovani *et al.*[13]	2 case–control studies and 7 cross-sectional studies	Biopsy, US, and transient elastography	13,462	4368	WMD	−0.01 (−0.03, 0.01)	**>0.05**	92.2	0.000	NA
BMD at the femur	Mantovani *et al.*[13]	1 case–control studies, 6 cross-sectional studies	Biopsy, US, and transient elastography	17,071	5151	WMD	−0.01 (−0.02, 0.01)	>0.05	94.3	0.000	NA
BMD at the pelvis	Mantovani *et al.*[13]	1 case–control studies and 4 cross-sectional studies	Biopsy, US, and transient elastography	1446	5930	WMD	0.02 (−0.01, 0.05)	>0.05	87.9	0.000	NA
Osteoporotic fractures	Mantovani *et al.*[13]	2 cross-sectional studies	Biopsy, US, and transient elastography	10,456	NA	OR	1.43 (1.00, 1.44)	0.051	55.1	0.083	0.008*
BMD at all anatomical sites	Upala *et al.*[46]	4 cross-sectional studies	NR	1021	490	MD	0.021 (−0.004, 0.045)	0.098	NA	NA	0.62
Skeletal muscle mass	Cai *et al.*[63]	6 cross-sectional studies and 1 cohort studies	Biopsy, US, FLI, HIS, LAI, CNS, LFS, and NAS	29,533	7934	WMD	−1.77 (−2.39, −1.15)	0.000	97.8	0.000	0.835
BMD in obese adolescent	Sun *et al.*[61]	6 case–control studies	Biopsy, US, and MRI	453	217	WMD	−0.03 (−0.05, −0.02)	0.000	60.2	0.039	NA
Z-scores	Sun *et al.*[61]	6 case–control studies	Biopsy, US, and MRI	453	217	WMD	−0.26 (−0.37, −0.14)	0.000	26.9	0.233	NA
Mortality											
ACM	Liu *et al.*[57,58]	12 cohort studies	NR	498,259	24,188	HR	1.34 (1.17, 1.54)	0.000*	80.0	0.000	>0.05
CVD mortality	Liu *et al.*[57,58]	7 cohort studies	NR	471,849	5541	HR	1.13 (0.92, 1.38)	0.237*	57.5	0.028	0.405*
Cancer mortality	Liu *et al.*[57,58]	5 cohort studies	NR	465,112	6924	HR	1.05 (0.89, 1.25)	0.562*	35.3	0.186	0.300*

(Continued)

Table 1. (Continued)

Health outcomes	Author	Studies (*n*)	NAFLD diagnosis	Participants (*n*)	Cases (*n*)	Type of metric	Effect size		Heterogeneity		Small-study effect
							95% CI	*p* value	I^2	*p* value	
Hepatocellular carcinoma mortality	Liu *et al.*[57,58]	2 cohort studies	NR	470,775	255	HR	2.53 (1.23, 5.18)	0.000*	81.2	<0.01	NA
ACM in CVD patients	Wu *et al.*[42]	5 cohort studies	Biopsy, US, and liver enzyme	21,186	3186	HR	1.14 (0.99, 1.32)	0.076	65.4	0.08	0.109
CVD mortality	Wu *et al.*[42]	5 cohort studies	Biopsy, US, and liver enzyme	21,803	1903	HR	1.10 (0.86, 1.41)	0.440	64.9	0.002	0.378
COVID-19 mortality	Singh *et al.*[79]	2 cohort studies	NR	7042	NA	OR	1.01 (0.65, 1.58)	0.96	0.0	0.76	NA
ACM in female	Khalid *et al.*[67]	1 cross-sectional studies and 9 cohort studies	Biopsy, US, and liver enzyme	10,877	NA	OR	1.65 (1.12, 2.43)	0.012	98.7	<0.0001	NA
Metabolic disorders											
T2D	Mantovani *et al.*[76,77]	26 cohort studies	US and CT	418,564	22,67	HR	2.19 (1.93, 2.48)	0.000*	91.2	0.000	0.054*
Metabolic syndrome	Ballestri *et al.*[34]	12 cohort studies	NR	81,411	14,514	RR	2.25 (1.62, 3.13)*	<0.001*	99.3*	0.000*	0.219*
Diabetic retinopathy in T2D	Song *et al.*[80]	9 cross-sectional studies	US	7170	2671	OR	0.94 (0.51, 1.71)	0.83*	96.0	<0.00001	0.902*
Urological disorders											
Urolithiasis	Wijarnpreecha *et al.*[51-53]	7 cross-sectional studies and 1 cohort study	US and CT	238,400	NA	OR	1.81 (1.29, 2.56)	0.0007	28.8	0.25	0.74*
Urinary system cancers	Mantovani *et al.*[76,77]	4 cohort studies	US and ICD code	120,851	414	HR	1.33 (1.04, 1.70)	0.025*	10.4	0.35	0.537*
Nephrological disorders											
Prevalent CKD	Musso *et al.*[30]	16 cross-sectional studies	Biopsy, US, and liver enzyme	27,012	2694	OR	2.12 (1.69, 2.66)	<0.001*	77.0	<0.00001	0.473
Incident CKD	Musso *et al.*[30]	12 longitudinal studies	Biopsy, US, and liver enzyme	28,680	2141	HR	1.79 (1.65, 1.95)	<0.001*	0.0	0.83	0.644
Albuminuria	Wijarnpreecha *et al.*[51-53]	17 cross-sectional studies and 2 cohort studies	US, FLI, and transient elastography	24,804	NA	OR	1.67 (1.32, 2.11)	0.000*	76.0	0.000*	0.08

(Continued)

Table 1. (Continued)

Health outcomes	Author	Studies (*n*)	NAFLD diagnosis	Participants (*n*)	Cases (*n*)	Type of metric	Effect size		Heterogeneity		Small-study effect
							95% CI	*p* value	I^2	*p* value	
Serum marker disorders											
Homocysteine level	Dai *et al.*[35]	6 cross-sectional studies and 2 case–control study	Biopsy	935	538	SMD	0.66 (0.41, 0.92)	0.000	64.3	0.007	0.698
Folate level	Dai *et al.*[35]	5 cross-sectional studies and 2 case–control study	Biopsy	802	331	SMD	−0.26 (−0.69, 0.17)	<0.05	85.7	0.000	0.344
Vitamin B12	Dai *et al.*[35]	5 cross-sectional studies and 2 case–control study	Biopsy	802	331	SMD	0.28 (−0.35, 0.92)	<0.05	93.4	0.000	0.215
MPV	Madan *et al.*[38]	8 observational studies	Biopsy and US	1428	842	SMD	0.612 (0.286, 0.938)	0.000	0.0	0.723	0.11
Circulating leptin	Polyzos *et al.*[39]	24 cross-sectional studies	Biopsy	2006	775	SMD	0.64 (0.42, 0.86)	<0.0001	77.6	<0.0001	0.98
Serum ferritin	Du *et al.*[43]	3 case–control studies	Biopsy and US	225	101	SMD	1.01 (0.89, 1.13)	<0.0001	88.4	0.000	0.602
C-reactive protein	Liu *et al.*[57,58]	19 case–control studies	Biopsy and US	5313	2414	SMD	1,25 (0.81, 1.68)	<0.00001	98.0	<0.00001	0.0023*
Serum resisting level	Han *et al.*[72]	8 cross-sectional studies and 8 case–control studies	Biopsy and US	1961	1239	SMD	0.52 (0.00, 1.04)	0.047	95.9	0.000	NA
Visfatin Levels	Ismaiel *et al.*[74]	3 cross-sectional studies and 5 case–control studies, 1 cohort	Biopsy, US, and CT	946	523	MD	3.361 (−0.175, 6.897)	<0.05	97.1	<0.001	NA
Vitamin D deficiency	Eliades *et al.*[29]	9 observational studies	NR	13,722	8520	OR	1.26 (1.17, 1.35)	<0.001*	65.2	0.003	0.32
Respiratory system disorder											
Predicted FEV1	Mantovani *et al.*[16,59,60]	5 cross-sectional studies	US and LFS	37,567	12,713	WMD	−2,43 (−3.28, −1.58)	<0.0001	69.7	0.010	0.13
Predicted FVC	Mantovani *et al.*[16,59,60]	4 cross-sectional studies	US and LFS	25,829	9143	WMD	−2.96 (−4.75, −1.17)	<0.0001	91.7	0.000	0.21*
Lung cancer	Mantovani *et al.*[76,77]	5 cohort studies	US and ICD code	140,014	837	HR	1.30 (1.14, 1.48)	0.000*	0.0	0.94	0.165*
Other health outcomes											
Severe COVID-19	Hegyi *et al.*[73]	3 cohort studies	NR	7284	997	OR	5.22 (1.94, 14.03)	0.001*	85.1	0.001	0.921*
ICU admission of COVID-19	Hegyi *et al.*[73]	3 cohort studies	NR	7433	578	OR	2.29 (0.79, 6.63)	0.166*	85.1	0.001	0.122*

(Continued)

Table 1. (Continued)

Health outcomes	Author	Studies (*n*)	NAFLD diagnosis	Participants (*n*)	Cases (*n*)	Type of metric	Effect size		Heterogeneity		Small-study effect
							95% CI	*p* value	I^2	*p* value	
Depression	Xiao *et al.*[82]	4 cohort studies	NR	38,047	3305	OR	1.29 (1.02, 1.64)	0.03*	73.0	0.01	0.420*
Endothelial dysfunction	Fan *et al.*[36]	2 cross-sectional studies and 9 case–control studies	Biopsy and US	906	545	WMD	−4.82 (−5.63, −4.00)	0.000	57.5	0.009	0.188
Carotid–femoral PWV	Jaruvongvanich *et al.*[37]	6 cross-sectional studies and 1 case–control study	Biopsy, US, and CT	3957	783	MD	0.75 (0.37, 1.12)	0.000	89.0	<0.01	0.013
Brachial–ankle PWV	Jaruvongvanich *et al.*[37]	8 cross-sectional studies	Biopsy, US, and CT	NA	NA	MD	0.82 (0.57, 1.07)	0.000	92.0	<0.01	0.97
Augmentation index	Jaruvongvanich *et al.*[37]	5 cross-sectional studies and 1 case–control study	Biopsy, US, and CT	12509	3334	MD	2.54 (0.07, 5.01)	0.044	73.0	0.01	0.11
Breast cancer	Mantovani *et al.*[76,77]	4 cohort studies	US and ICD code	85,827	1347	HR	1.39 (1.13, 171)	0.002*	0.0	0.41	0.531*
Thyroid cancer	Mantovani *et al.*[76,77]	2 cohort studies	US and ICD code	64,732	776	HR	2.63 (1.27, 5.45)	0.009*	0.0	0.72	NA
Female genital organ cancers	Mantovani *et al.*[76,77]	4 cohort studies	US and ICD code	85,827	558	HR	1.62 (1.13, 2.32)	0.008*	40.8	0.15	0.296*
Prostate cancer	Mantovani *et al.*[76,77]	5 cohort studies	US and ICD code	140,014	1002	HR	1.16 (0.82, 1.64)	0.39*	62.5	0.032	0.142*
Hematological cancers	Mantovani *et al.*[76,77]	2 cohort studies	US and ICD code	NA	NA	HR	1.47 (0.69, 3.12)	0.47*	62.3	0.029	NA

C-IMT, carotid intima-media thickness; US, ultrasound; CT, computed tomography; FLI, fatty liver index; HIS, hepatic steatosis index; ICD, International Classification of Diseases; LAI, liver attenuation index; CNS, comprehensive NAFLD score; LFS, liver fat score; NFS, NAFLD fibrosis score; MRI, magnetic resonance imaging; CAC, coronary artery calcification; CVD, cardiovascular disease; CAD, coronary artery disease; LEVF, left ventricular ejection fraction; E/e' ratio, early mitral velocity/early diastolic tissue velocity; E/A ratio, early mitral velocity/late mitral velocity ratio; BSA, body surface area; EFT, epicardial fat tissue; GLS, global longitudinal strain; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma, IP, intestinal permeability; AP, acute pancreatitis, BMD, bone mineral density; ACM, all-cause mortality; T2D, type-2 diabetes; CKD, chronic kidneys disease; MPV, mean platelet volume; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICU, intensive care unit; PWV, posterior wall velocity; NR, not reported.
*The result was reanalyzed.

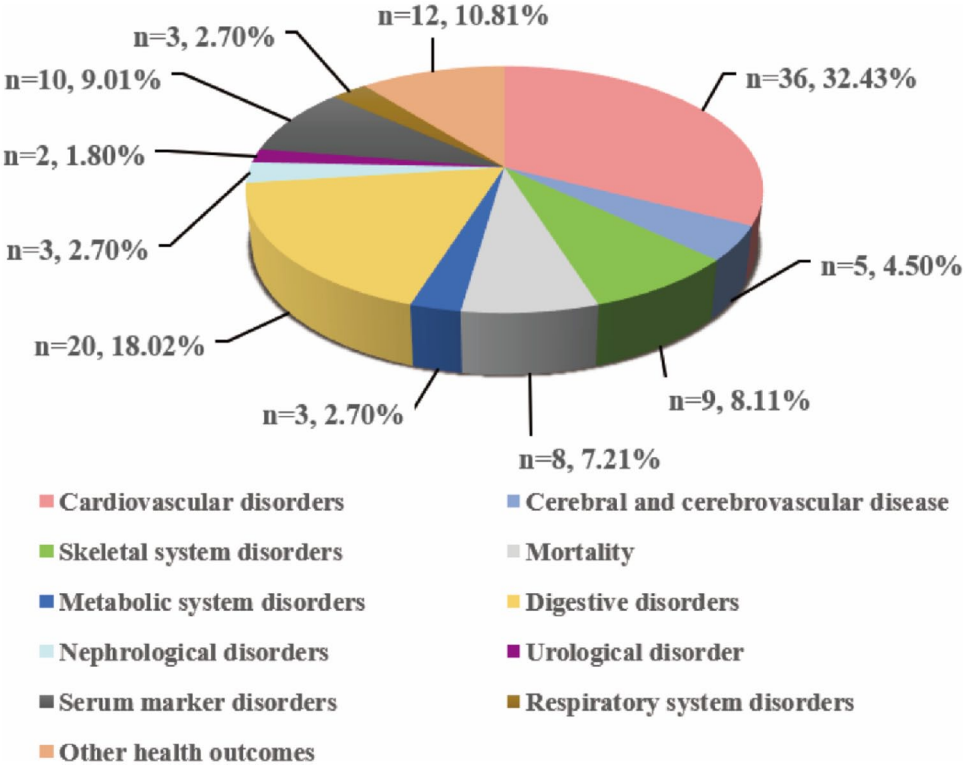

Figure 2. Map of achievements associated with NAFLD.

epidemiologic evidence, and 58 (52.25%) outcomes were graded as weak epidemiologic evidence (Figure 4).

Discussion

Main findings and interpretation

Our umbrella review provides a comprehensive overview of the association between NAFLD and other health outcomes based on the existing evidence from identified 54 observational studies with 111 unique outcomes. We also critically evaluated the strength of evidence for all these associations with the criteria broadly applied to assess the epidemiologic evidence in the various field[22–26] and the quality of methodology of each publication, including in the current review. We found that NALFD increased the risk of 85 health outcomes that contained cardiovascular disorders, cerebral and cerebrovascular disorders, digestive disorders, nephrological disorders, urological disorders, metabolic disorders, mortality, skeletal system disorders, serum marker disorders, respiratory system disorders, and other health outcomes. However, 26 health outcomes had no relationship with NALFD and could not be assessed the epidemiologic evidence in this study. Only four outcomes (carotid intimal medial thickness (C-IMT), peak A velocity, left ventricle end-diastolic diameter (LVEDD), and incident CKD in adult patients) showed high epidemiologic evidence. The 81 remaining associations were either rated as moderate epidemiologic evidence or weak epidemiologic evidence. Heterogeneity and small-study effects were the two main reasons for the evidence rating downgrade in our study.

NAFLD increased C-IMT which is considered as a marker of subclinical atherosclerosis with high epidemiologic evidence in the review. The potential mechanism seems to relate to high oxidative stress caused by steatosis-stimulated fatty-acid oxidation in the liver, increased insulin resistance, and macrophage activation.[7,83,84] Through early detection and intervention, subclinical atherosclerosis can be controlled and even reversed.[85] Therefore, for NAFLD, it is important to identify the C-IMT earlier. The cardiac function and

Table 2. Assessments of AMSTAR2 scores.

References	AMSTAR 2 checklist																Overall assessment quality
	NO.1	NO.2	NO.3	NO.4	NO.5	NO.6	NO.7	NO.8	NO.9	NO.10	NO.11	NO.12	NO.13	NO.14	NO.15	NO.16	
Madan *et al.*[33]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Zhou *et al.*[54]	Y	N	Y	PY	Y	Y	PY	PY	N	N	Y	Y	Y	Y	Y	Y	Critically low
Ampuero *et al.*[31]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	N	Y	Y	N	Critically low
Jaruvongvanich *et al.*[37]	Y	Y	Y	PY	Y	Y	PY	PY	N	N	Y	Y	N	Y	Y	Y	Critically low
Targher *et al.*[41]	Y	Y	Y	PY	Y	Y	PY	Y	Y	N	Y	N	Y	Y	Y	N	Critically low
Wu *et al.*[42]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	N	Y	N	Y	Critically low
Veracruz *et al.*[81]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	Y	Y	Y	Y	Critically low
Borges-Canha *et al.*[55]	Y	N	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Bonci *et al.*[32]	Y	N	Y	PY	Y	Y	PY	PY	N	N	Y	N	N	Y	Y	Y	Critically low
Oikonomidou *et al.*[78]	Y	Y	Y	Y	Y	Y	PY	PY	Y	N	Y	N	N	Y	Y	Y	Critically low
Wijarnpreecha *et al.*[51,52,53]	Y	N	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Wijarnpreecha *et al.*[71]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	Y	Y	N	Y	Critically low
Cai *et al.*[63,64]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Critically low
Liu *et al.*[57,58]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	N	Y	N	Y	Critically low
Yao *et al.*[48]	Y	N	Y	PY	Y	Y	PY	PY	N	N	Y	N	N	N	Y	Y	Critically low
Mantovani *et al.*[76,77]	Y	Y	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Ballestri *et al.*[34]	Y	N	Y	PY	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Critically low
Song *et al.*[80]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Qin and Ding[40]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	N	Y	N	Y	Critically low
Wongjarupong *et al.*[47]	Y	Y	Y	Y	Y	Y	PY	PY	Y	N	Y	N	Y	Y	Y	Y	Low
Stine *et al.*[50]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	Y	Y	Y	Y	Critically low
Liu *et al.*, 2021	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	N	N	N	Y	Critically low

(Continued)

Table 2. (Continued)

References	AMSTAR 2 checklist																Overall assessment quality
	NO.1	NO.2	NO.3	NO.4	NO.5	NO.6	NO.7	NO.8	NO.9	NO.10	NO.11	NO.12	NO.13	NO.14	NO.15	NO.16	
Chen *et al.*[56]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Munck *et al.*[66]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	Y	Y	Y	Y	Critically low
Lin *et al.*[75]	Y	Y	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Xue *et al.*[62]	Y	N	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Váncsa *et al.*[70]	Y	Y	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Chen *et al.*[65]	Y	N	Y	PY	Y	N	PY	Y	Y	N	Y	Y	Y	N	Y	Y	Critically low
Musso *et al.*[30]	Y	Y	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Wijarnpreecha *et al.*[51,52,53]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Wijarnpreecha *et al.*[51,52,53]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	N	Y	Y	Y	Critically low
Mantovani *et al.*[13]	Y	Y	Y	PY	Y	N	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Low
Upala *et al.*[46]	Y	Y	Y	PY	Y	Y	N	PY	Y	N	Y	Y	N	Y	Y	Y	Critically low
Cai *et al.*, 2019	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Sun *et al.*[61]	Y	N	Y	PY	N	Y	PY	PY	Y	N	Y	N	N	Y	N	Y	Critically low
Fan *et al.*[36]	Y	N	Y	PY	Y	Y	Y	PY	Y	N	Y	N	N	Y	Y	Y	Critically low
Jaruvongvanich *et al.*[37]	Y	Y	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Low
Hu *et al.*[49]	Y	N	Y	PY	N	Y	PY	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Mahfood Haddad *et al.*[44]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Liu *et al.*[57,58]	Y	N	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Singh *et al.*[79]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	N	N	Y	Y	Critically low
Khalid *et al.*[67]	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	N	Y	Y	Y	Y	Critically low
Dai *et al.*[35]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	N	Y	Y	Y	Critically low
Madan *et al.*[38]	Y	N	N	PY	N	Y	PY	PY	Y	N	Y	Y	N	N	Y	Y	Critically low

(Continued)

Table 2. (Continued)

References	AMSTAR 2 checklist																Overall assessment quality
	NO.1	NO.2	NO.3	NO.4	NO.5	NO.6	NO.7	NO.8	NO.9	NO.10	NO.11	NO.12	NO.13	NO.14	NO.15	NO.16	
Polyzos *et al.*[39]	Y	N	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Du *et al.*[43]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	N	Y	Y	Critically low
Liu *et al.*[68,69]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	Y	N	Critically low
Han *et al.*[72]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	N	Y	Y	Y	Critically low
Mantovani *et al.*[76,77]	Y	Y	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Ismaiel *et al.*[74]	Y	N	Y	PY	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Critically low
Eliades *et al.*[29]	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	N	N	Y	Y	Y	Critically low
Mantovani *et al.*[16,59,60]	Y	Y	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Low
Hegyi *et al.*[73]	Y	Y	Y	PY	Y	Y	PY	Y	Y	N	Y	N	Y	Y	Y	Y	Critically low
Xiao *et al.*[82]	Y	N	Y	PY	Y	Y	PY	Y	N	N	Y	Y	N	Y	Y	Y	Critically low

AMSTAR 2 checklist (items in italic are considered critical):
1, PICO description; 2, protocol registered before the commencement of the review; 3, study design included in the review; 4, adequacy of the literature search; 5, two authors study selection; 6, two authors study extraction; 7, list for excluding individual studies; 8, included studies descripted in detail; 9, risk of bias for the single studies that included in the review; 10, source of funding of primary studies; 11, appropriateness of meta-analytical methods; 12, impact of risk of bias of single studies on the results of the meta-analysis; 13, consideration of risk of bias when interpreting the results of the review; 14 explanation and discussion of the heterogeneity observed; 15, assessment of presence and likely impact of publication bias; 16, funding sources and conflict of interest declared.
Abbreviations: Y, yes; PY, partial yes; N, no.
High: 0–1 non-critical weakness. The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
Moderate: >1 non-critical weakness. The systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
Low: 1 critical flaw with or without non-critical weaknesses. The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
Critically low: >1 critical flaw with or without non-critical weaknesses. The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.
No 2, 4, 7, 9, 11, 13, and 15 are the critical items.

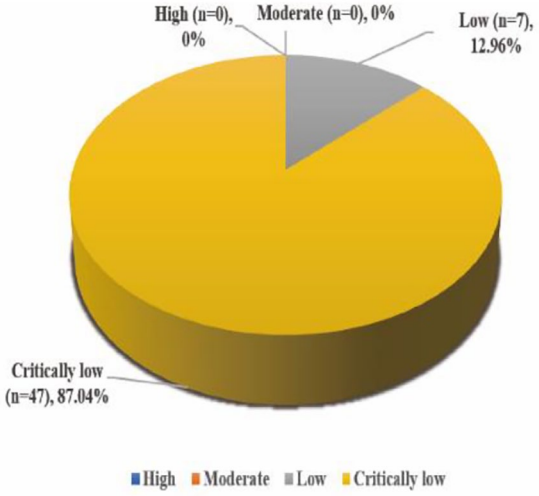

Figure 3. Map of results of AMSTAR 2.

structure were also damaged by NAFLD. We demonstrated the association between NAFLD and peak A velocity and LVEDD was both graded as high. In NAFLD patients, the role of pro-inflammatory cytokines, insulin resistance, and dyslipidemia acts together on the cardiac metabolism and function,[86–88] which directly causes the impairment on the heart.

In 2020, a large database analysis in Germany, comprised of 48,057 patients with NAFLD and 48,057 patients without NAFLD, supported that NAFLD constitutes an independent risk factor for CKD.[89] Similarly, in our umbrella review, the incidence of CKD was also increased by NAFLD with high epidemiologic evidence. There exists a common pro-inflammatory and profibrotic mechanism of disease progression in both NAFLD and CKD; furthermore, kidney-liver crosstalk also appears in NAFLD.[89] In addition to insulin resistance, pro-inflammatory factors, oxidative stress, the rein-angiotensin-aldosterone system also plays a role in the pathogenesis.[90–92]

We noted that no study included in this umbrella review showed high/moderate methodologic evidence and only seven studies showed low methodological quality according to AMSTAR 2 criteria. The most critical flaws were the absence of registered protocol, the literature search's inadequacy, and the list for excluding individual studies. Eighty-five outcomes showed remarkable heterogeneity between studies. We concluded that this may be caused by several factors such as NAFLD severity, sex, the diagnosis of NAFLD, the study design, and body mass index, resulting in unreliable results. Among 111 health outcomes, 19 outcomes presented publication bias detected by Egger's test. The main reason for publication bias is that positive results are easier to publish than negative results, leading to incomplete literature included in the meta-analysis. Another common reason is that the study sample size is too small.

Strength and limitations

Our umbrella review had several strengths. To our knowledge, it is the first umbrella review of observational meta-analysis and provides a comprehensive overview of the associations of NAFLD and health outcomes. A strong search strategy and data extraction were performed by two authors independently which made the result more reliable. Furthermore, we used validated AMSTR 2 tool to evaluate the methodological quality in our umbrella review.

However, several limitations should be considered in the interpretation of our umbrella review. We did not evaluate the quality of the primary studies because it was beyond the scope of the current umbrella review. We conducted the review based on the published meta-analyses with the largest number of studies at present, and we might have missed some individual studies, which could have an influence on the results. In this umbrella review, 21 health outcomes publication bias could not be assessed due to the limited number of primary studies (less than two) and missing data which indicates unreliable results. Thus, more research is needed to investigate these associations that were based on small number of included studies.

Another limitation to consider is that we could not conduct the subgroup analysis in this study (eg. sex differences, pre-menopausal, and post-menopausal women) owing to lack of raw data. As comprehension evolves, sex differences, and menopausal status are increasingly apparent in the prevalence, risk factors, progression, and outcomes in NAFLD. Numerous studies have indicated compare to women, men have higher risk and prevalence of NAFLD.[93,94] But the prevalence of NAFLD is equal in men and post-menopausal women.[95] A meta-analysis pointed out that after age 50, women have a higher risk of

Table 3. The strength of epidemiologic evidence of 111 unique health outcomes.

Health outcomes	Author, year	Precision of the estimate		Consistency of results	No evidence of small-study effects ($P > 0.1$)	Grade
		> 1000 disease cases	$p < 0.001$	$I^2 < 50\%$ and Cochran Q-test $p > .10$		
Cardiovascular disorders						
C-IMT in adult patients	Madan *et al.*[33]	Yes	Yes	Yes	Yes	High
Carotid plaque in adult patients	Madan *et al.*[33]	Yes	No	Yes	Yes	Weak
C-IMT in pediatric patients	Madan *et al.*[33]	No	No	Yes	Yes	Weak
CAC	Zhou *et al.*[54]	Yes	Yes	No	No	Weak
Arterial stiffness	Zhou *et al.*[54]	Yes	Yes	No	Yes	Moderate
Endothelial dysfunction	Zhou *et al.*[54]	No	No	No	No	Weak
Subclinical atherosclerosis	Ampuero *et al.*[31]	No	Yes	Yes	Yes	Moderate
CAC score > 0	Jaruvongvanich *et al.*[37]	No	Yes	No	No	Weak
CAC score > 100	Jaruvongvanich *et al.*[37]	No	No ($p > 0.05$)	Yes	Yes	NA
Fatal CVD	Targher *et al.*[41]	Yes	No ($p > 0.05$)	No	Yes	NA
Fatal and non-fatal CVD	Targher *et al.*[41]	Yes	No	No	Yes	Weak
Non-fatal CVD	Targher *et al.*[41]	No	Yes	No	Yes	Weak
CAD	Wu *et al.*[42]	No	No	No	Yes	Weak
CVD	Veracruz *et al.*[81]	Yes	Yes	No	Yes	Moderate
LVEF	Borges-Canha *et al.*[55]	Yes	No ($p > 0.05$)	No	Yes	NA
Peak E velocity	Borges-Canha *et al.*[55]	Yes	No ($p > 0.05$)	No	No	NA
E/e' ratio	Borges-Canha *et al.*[55]	Yes	Yes	No	Yes	Moderate
Peak A velocity	Borges-Canha *et al.*[55]	Yes	Yes	Yes	Yes	High
E/A ratio	Borges-Canha *et al.*[55]	Yes	Yes	No	Yes	Moderate
Isovolumic relaxation time	Borges-Canha *et al.*[55]	No	No	No	Yes	Weak
Deceleration time	Borges-Canha *et al.*[55]	Yes	Yes	No	No	Weak

(Continued)

Table 3. (Continued)

Health outcomes	Author, year	Precision of the estimate		Consistency of results	No evidence of small-study effects ($P > 0.1$)	Grade
		> 1000 disease cases	$p < 0.001$	$I^2 < 50\%$ and Cochran Q-test $p > .10$		
Left ventricle mass	Borges-Canha *et al.*[55]	Yes	Yes	No	No	Weak
Left ventricle end-diastolic diameter	Borges-Canha *et al.*[55]	Yes	Yes	Yes	Yes	High
Left ventricle end-systolic diameter	Borges-Canha *et al.*[55]	Yes	No ($p > 0.05$)	No	Yes	NA
Left atrium diameter	Borges-Canha *et al.*[55]	Yes	Yes	No	Yes	Moderate
Posterior wall thickness	Borges-Canha *et al.*[55]	Yes	Yes	No	Yes	Moderate
Interventricular septum thickness	Borges-Canha *et al.*[55]	Yes	Yes	No	Yes	Moderate
LV mass indexed to BSA	Bonci *et al.*[32]	No	Yes	No	No	Weak
LV mass indexed to height	Bonci *et al.*[32]	No	No ($p > 0.05$)	Yes	No	NA
EFT thickness	Oikonomidou *et al.*[78]	No	Yes	No	Yes	Weak
GLS	Oikonomidou *et al.*[78]	No	Yes	No	Yes	Weak
Diastolic cardiac dysfunction	Wijarnpreecha *et al.*[51,52,53]	No	Yes	No	No	Weak
Cardiac conduction defect	Wijarnpreecha *et al.*[71]	No	No	No	No	Weak
Atrial fibrillation	Cai *et al.*[63,64]	Yes	No	No	Yes	Weak
Epicardial adipose tissue	Liu *et al.*[57,58]	Yes	Yes	No	No	Weak
Hypertension and prehypertension	Yao *et al.*[48]	No	Yes	No	No	Weak
Cerebral and cerebrovascular disease						
Cerebrovascular accident	Hu *et al.*[49]	No	Yes	Yes	Yes	Moderate
Ischemic stroke	Hu *et al.*[49]	No	Yes	Yes	No	Weak
Cerebral hemorrhage	Hu *et al.*[49]	No	No	Yes	No	Weak
Stroke and cerebrovascular diseases	Veracruz *et al.*[81]	Yes	Yes	No	No	Weak

(Continued)

Table 3. (Continued)

Health outcomes	Author, year	Precision of the estimate		Consistency of results	No evidence of small-study effects ($P > 0.1$)	Grade
		> 1000 disease cases	$p < 0.001$	$I^2 < 50\%$ and Cochran Q-test $p > .10$		
Stroke	Mahfood Haddad *et al.*[44]	No	Yes	Yes	Yes	Moderate
Digestive disorder						
Gallstone disease	Qin and Ding[40]	Yes	No	No	No	Weak
Cholangiocarcinoma	Wongjarupong *et al.*[47]	Yes	Yes	No	Yes	Moderate
HCC with/without cirrhosis	Stine *et al.*[50]	Yes	No ($p > 0.05$)	No	Yes	NA
HCC without cirrhosis	Stine *et al.*[50]	Yes	No	No	Yes	Weak
ICC	Liu *et al.*, 2021	No	Yes	No	Yes	Weak
ECC	Liu *et al.*, 2021	No	Yes	No	Yes	Weak
Colorectal adenoma	Chen *et al.*[56]	No	No	Yes	Yes	Weak
Colorectal cancer	Liu *et al.*, 2021	No	Yes	No	No	Weak
Recurrent colorectal adenoma/cancer	Chen *et al.*[56]	No	No	Yes	Yes	Weak
Right colon tumors	Lin *et al.*[75]	Yes	Yes	No	Yes	Moderate
Left colon tumors	Lin *et al.*[75]	Yes	Yes	No	Yes	Moderate
Esophagus cancer	Mantovani *et al.*[76,77]	No	No	Yes	Yes	Weak
Stomach cancer	Mantovani *et al.*[76,77]	No	No	No	No	Weak
Pancreas cancer	Mantovani *et al.*[76,77]	No	No	Yes	Yes	Weak
IP by means of 5-6 h L/M or L/R	Munck *et al.*[66]	No	Yes	Yes	Yes	Moderate
IP by means of serum zonulin	Mu Munck *et al.*, 2020	No	Yes	No	Yes	Weak
Gastroesophageal reflux disease	Xue *et al.*[62]	No	Yes	No	No	Weak
Overall survival of AP	Váncsa *et al.*[70]	No	No ($p > 0.05$)	No	No	NA
Moderately severe/severe AP	Váncsa *et al.*[70]	No	No	No	No	Weak
Colorectal polyps	Chen *et al.*[65]	Yes	Yes	No	No	Weak

(Continued)

Table 3. (Continued)

Health outcomes	Author, year	Precision of the estimate		Consistency of results	No evidence of small-study effects ($P > 0.1$)	Grade
		> 1000 disease cases	$p < 0.001$	$I^2 < 50\%$ and Cochran Q-test $p > .10$		
Skeletal system disorders						
Total BMD	Mantovani *et al.*[13]	No	No ($p > 0.05$)	No	No	NA
BMD at the lumbar spine	Mantovani *et al.*[13]	Yes	No ($p > 0.05$)	No	No	NA
BMD at the femur	Mantovani *et al.*[13]	Yes	No ($p > 0.05$)	No	No	NA
BMD at the pelvis	Mantovani *et al.*[13]	Yes	No ($p > 0.05$)	No	No	NA
BMD at all anatomical sites	Upala *et al.*[46]	No	No ($p > 0.05$)	No	No	NA
Osteoporotic fractures	Mantovani *et al.*[13]	No	No ($p > 0.05$)	No	No	NA
Skeletal muscle mass	Cai *et al.*, 2019	Yes	Yes	No	Yes	Moderate
BMD in obese adolescent	Sun *et al.*[61]	No	Yes	No	No	Weak
Z-scores	Sun *et al.*[61]	No	Yes	Yes	No	Weak
Mortality						
ACM	Liu *et al.*[57,58]	Yes	Yes	No	No	Weak
CVD mortality	Liu *et al.*[57,58]	Yes	No ($p > 0.05$)	No	Yes	NA
cancer mortality	Liu *et al.*[57,58]	Yes	No ($p > 0.05$)	Yes	Yes	NA
Hepatocellular carcinoma mortality	Liu *et al.*[57,58]	No	Yes	No	No	Weak
ACM in CVD patients	Wu *et al.*[42]	Yes	No ($p > 0.05$)	No	Yes	NA
CVD mortality	Wu *et al.*[42]	Yes	No ($p > 0.05$)	No	Yes	NA
COVID-19 mortality	Singh *et al.*[79]	No	No ($p > 0.05$)	Yes	No	NA
ACM in female	Khalid *et al.*[67]	No	No	No	No	Weak
Metabolic system disorders						
T2D	Mantovani *et al.*[76,77]	Yes	Yes	No	No	Weak
Metabolic syndrome	Ballestri *et al.*[34]	Yes	Yes	No	Yes	Moderate

(Continued)

Table 3. (Continued)

Health outcomes	Author, year	Precision of the estimate		Consistency of results	No evidence of small-study effects ($P > 0.1$)	Grade
		> 1000 disease cases	$p < 0.001$	$I^2 < 50\%$ and Cochran Q-test $p > .10$		
Diabetic retinopathy in T2D	Song *et al.*[80]	Yes	No ($p > 0.05$)	No	Yes	NA
Urological disorder						
Urolithiasis	Wijarnpreecha *et al.*[51,52,53]	No	Yes	Yes	Yes	Moderate
Urinary system cancers	Mantovani *et al.*[76,77]	No	No	Yes	Yes	Weak
Nephrological						
Prevalent CKD	Musso *et al.*[30]	Yes	Yes	No	Yes	Moderate
Incident CKD	Musso *et al.*[30]	Yes	Yes	Yes	Yes	High
Albuminuria	Wijarnpreecha *et al.*[51,52,53]	No	Yes	No	No	Weak
Serum marker disorders						
Homocysteine level	Dai *et al.*[35]	No	Yes	No	Yes	Weak
Folate level	Dai *et al.*[35]	No	No ($p > 0.05$)	No	Yes	NA
Vitamin B12	Dai *et al.*[35]	No	No ($p > 0.05$)	No	Yes	NA
MPV	Madan *et al.*[38]	No	Yes	Yes	Yes	Moderate
Circulating leptin	Polyzos *et al.*[39]	No	Yes	No	Yes	Weak
Serum ferritin	Du *et al.*[43]	No	Yes	No	Yes	Weak
C-reactive protein, CRP	Liu *et al.*[68,69]	Yes	Yes	No	No	Weak
Serum resistin level	Han *et al.*[72]	Yes	No	No	No	Weak
Visfatin Levels	Ismaiel *et al.*[74]	No	No ($p > 0.05$)	No	No	NA
vitamin D deficiency	Eliades *et al.*[29]	Yes	Yes	No	Yes	Moderate
Respiratory system disorder						
Predicted FEV1	Mantovani *et al.*[16,59,60]	Yes	Yes	No	Yes	Moderate
Predicted FVC	Mantovani *et al.*[16,59,60]	Yes	Yes	No	Yes	Moderate

(Continued)

Table 3. (Continued)

Health outcomes	Author, year	Precision of the estimate		Consistency of results	No evidence of small-study effects ($P > 0.1$)	Grade
		> 1000 disease cases	$p < 0.001$	$I^2 < 50\%$ and Cochran Q-test $p > .10$		
Lung cancer	Mantovani *et al.*[76,77]	No	Yes	Yes	Yes	Moderate
Other health outcomes						
Severe COVID-19	Hegyi *et al.*[73]	No	No	No	Yes	Weak
ICU admission of COVID-19	Hegyi *et al.*[73]	No	No ($p > 0.05$)	No	Yes	NA
Depression	Xiao *et al.*[82]	Yes	No	No	Yes	Weak
Endothelial dysfunction	Fan *et al.*[36]	No	Yes	No	Yes	Weak
Carotid–femoral PWV	Jaruvongvanich *et al.*[37]	No	Yes	No	No	Weak
Brachial–ankle PWV	Jaruvongvanich *et al.*[37]	No	Yes	No	Yes	Weak
Augmentation index	Jaruvongvanich *et al.*[37]	Yes	No	No	Yes	Weak
Breast cancer	Mantovani *et al.*[76,77]	Yes	No	Yes	Yes	Weak
Thyroid cancer	Mantovani *et al.*[76,77]	No	No	Yes	No	Weak
Female genital organ cancers	Mantovani *et al.*[76,77]	No	No	Yes	Yes	Weak
Prostate cancer	Mantovani *et al.*[76,77]	Yes	No ($p > 0.05$)	No	Yes	NA
Hematological cancers	Mantovani *et al.*[76,77]	NO	No ($p > 0.05$)	No	No	NA

C-IMT, carotid intima-media thickness; CAC, coronary artery calcification; CVD, cardiovascular disease; CAD, coronary artery disease; LEVF, left ventricular ejection fraction; E/e' ratio, early mitral velocity/early diastolic tissue velocity; E/A ratio, early mitral velocity/late mitral velocity ratio; BSA, body surface area; EFT, epicardial fat tissue; GLS, global longitudinal strain; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma, IP, intestinal permeability; AP, acute pancreatitis, BMD, bone mineral density; ACM, all-cause mortality; T2D, type-2 diabetes; CKD, chronic kidneys disease; MPV, mean platelet volume; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; ICU, intensive care unit; PWV, posterior wall velocity.
Note. The strength of epidemiologic evidence was rated as follows:
High, if all criteria were satisfied: precision of the estimate ($p < .001$ and >1000 disease cases), consistency of results ($I^2 < 50\%$ and Cochran Q-test $p > .10$), and no evidence of small-study effects ($p > .10$).
Moderate, if a maximum of 1 criterion was not satisfied and a $p < .001$ was found.
Weak, in other cases ($p < .05$).
NA, p values are greater than 0.05, so the epidemiologic quality of these meta cannot be rated.

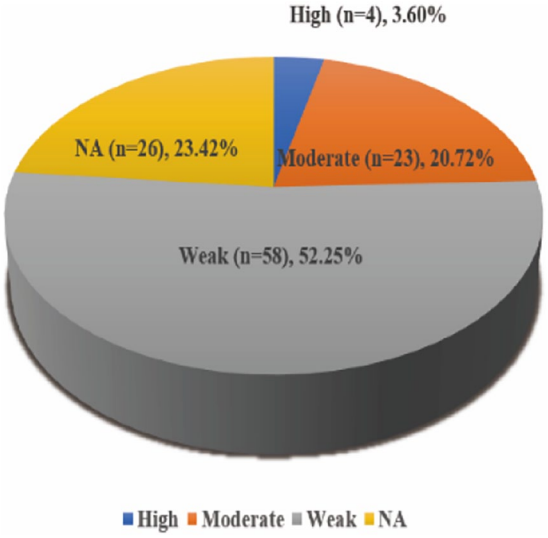

Figure 4. Map of results of evidence assessment.

developing advanced fibrosis than men.[96] However, several studies have shown that women have a higher incidence of NAFLD in early menarche and a higher risk of NASH and advanced fibrosis.[97,98] Almost all of the included meta-analyses did not distinguish between sex, pre-menopausal, and post-menopausal women in the included participants, which made it difficult to re-analyze the results according to the sex difference and menopausal status. However, we recognize the importance of sex difference and menopausal status and will focus on this aspect in future studies.

Conclusion

In summary, 54 studies explored 111 unique health outcomes; only four outcomes showed high epidemiologic evidence with statistical significance. NAFLD may be related to the increased risk of C-MIT, peak A velocity, LVEDD, and incident CKD in adult patients. However, more robust studies and investigations are needed to achieve high epidemiologic evidence for the associations between NAFLD and health outcomes.

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Author contributions

Lixian Zhong: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.
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Availability of data and material

The data used to support the findings of this study are included within the article. The primary data used to support the findings of this study are available from the corresponding author upon request.

Supplemental material

Supplemental material for this article is available online.

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