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 < 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. Forty-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

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 diseases7,8 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 been conducted to explore the relationship between NAFLD and health outcomes.
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 Steatohepatides’ OR ‘Steatohepatides, 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. The parameters consist of the following criteria: (1) precision of the estimate \( p \) value for the estimate \(< 0.001 \) and the number of cases \( \geq 1000 \); (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 \( (\text{eg. heterogeneity and publication bias}) \) with a random-effects model whenever possible. When the \( p \) value was < 0.05, the total impacts of pooled meta-analyses were considered significant. \( F \) 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 \( F \) and \( p \) 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 \( (F < 50\% \) and \( p \) value for Cochran \( Q \)-test > 0.1) whereas 85 \( (76.58\%) \) health outcomes showed significant heterogeneity \( (F \geq 50\% \) 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 > 0.1) while 19 health outcomes presented publication bias \( (p \) value for Egger’s test < 0.1).
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       | p value           |
|                                              |                               |                                                 |                                      |                  |           |                | p value     |               |                   |
| Cardiovascular disorders                     |                               |                                                 |                                      |                  |           |                |             |               |                   |
| C-IMT in adult patients                      | Madan et al.                  | 20 observational studies                       | Biopsy and US                        | 19,274           | 8652      | SMD            | 0.94 [0.78, 1.16] | <0.001 | 0.0       | 0.754            | 0.14             |
| C-IMT in pediatric patients                 | Madan et al.                  | 13 observational studies                      | Biopsy and US                        | 14,445           | 5399      | OR             | 1.77 [1.21, 2.58] | 0.003 | 0.0       | 0.561            | 0.76             |
| C-IMT in pediatric patients                 | Madan et al.                  | 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.                   | 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.                   | 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.                   | 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.                | 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.         | 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.         | 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.                | 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.                | 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.                | 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.                     | 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       | 0.06             | 0.248             |
| CVD                                          | Veracruz et al.               | 12 cross-sectional studies, 16 cohort 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.           | 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)
| Health outcomes       | Author                        | Studies (n) | NAFLD diagnosis  | Participants (n) | Cases (n) | Type of metric | Effect size | 95% CI             | p value | Heterogeneity | Small-study effect |
|-----------------------|-------------------------------|-------------|------------------|------------------|-----------|----------------|-------------|-------------------|---------|---------------|---------------------|
| Peak E velocity       | Borges-Canha et al.25         | 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.25         | 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.25         | 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.25         | 12 cross-sectional studies | Biopsy, US, and CT | 25,149          | 17,461    | MD             | -0.15     | (-0.22, -0.08)   | <0.00001| 94.0          | <0.0001 0.845*      |
| Isovolumic relaxation time | Borges-Canha et al.25         | 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.25         | 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.25         | 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.25 | 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.25 | 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.25         | 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.25         | 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.25       | 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.35               | 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.35               | 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.39         | 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.39         | 3 observational studies | Biopsy      | 146            | 67        | MD             | -3.17     | (-5.09, -1.24)   | <0.001 | 89.0          | 0.0001 0.875*       |
| Health outcomes                                      | Author                                  | Studies (n)                          | NAFLD diagnosis                  | Participants (n) | Cases (n) | Type of metric | Effect size               | Heterogeneity      | Small-study effect |
|-----------------------------------------------------|-----------------------------------------|-------------------------------------|----------------------------------|------------------|-----------|----------------|--------------------------|--------------------|-------------------|
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Diastolic cardiac dysfunction                        | Wijarnpreecha et al.                   | 12 cross-sectional studies          | US, CT, and ICD code             | 280,645          | NA        | OR             | 2.02 [1.47, 2.79]        | <0.0001            | 89.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Cardiac conduction defect                            | Wijarnpreecha et al.                   | 3 cross-sectional studies           | US, CT, and ICD code             | 3651             | NA        | OR             | 5.17 [1.34, 20.01]       | 0.02               | 96.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Atrial fibrillation                                  | Cai et al.                             | 6 cohort studies                    | US, CT, and FLI                  | 613,715          | 7271      | RR             | 1.19 [1.07, 1.31]        | 0.01*              | 54.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Epicardial adipose tissue                            | Liu et al.                             | 13 case-control studies             | NR                               | 4540             | 2260      | SMD            | 0.73 [0.51, 0.94]        | <0.001             | 88.6              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Hypertension and prehypertension                     | Yao et al.                             | 5 observational studies             | NR                               | 36,534           | NA        | OR             | 1.30 [1.14, 1.47]        | 0.000              | 65.6              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Cerebral and cerebrovascular disease                 | Hu et al.                              | 2 case-control studies and 3 cohort studies | NR                                 | 6183             | 390       | OR             | 2.32 [1.84, 2.93]        | <0.001             | 0.0               |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Cerebrovascular accident                             | Hu et al.                              | 2 case-control studies and 3 cohort studies | NR                                 | 4009             | 313       | OR             | 2.51 [1.92, 3.28]        | <0.001             | 0.0               |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Ischemic stroke                                      | Hu et al.                              | 2 case-control studies and 3 cohort studies | NR                                 | 1980             | 51        | OR             | 1.85 [1.05, 3.27]        | 0.034              | 0.0               |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Cerebral hemorrhage                                  | Hu et al.                              | 2 cohort studies                    | NR                               | 138,213          | 1444      | OR             | 1.95 [1.36, 2.79]        | 0.000              | 76.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Stroke and cerebrovascular diseases                  | Veracruz et al.                        | 16 cohorts                          | Biopsy, US, CT, and FLI          | 34,336           | 29,314    | RR             | 2.08 [1.72, 2.51]        | <0.000001         | 91.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Stroke                                              | Mahfood Haddad et al.                  | 3 cohort studies                    | NR                               | 2241             | NA        | RR             | 2.09 [1.46, 2.98]*       | <0.001*            | 14.8*             |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Digestive disorder                                  | Qin and Ding                           | 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              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Gallstone disease                                    | Wongjarupong et al.                    | 7 cross-sectional studies           | NR                               | 138,213          | 1444      | OR             | 1.95 [1.36, 2.79]        | 0.000              | 76.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| Cholangiocarcinoma                                   | Stine et al.                           | 12 observational studies            | Biopsy and US                    | 145,512          | 20,900    | OR             | 1.43 [0.77, 2.65]        | 0.25               | 99.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| HCC with/without cirrhosis                           | Stine et al.                           | 2 cross-sectional studies and 5 cohort studies | Biopsy and US                    | 23,059           | 3567      | OR             | 2.41 [1.27, 5.35]        | 0.009              | 95.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
| HCC without cirrhosis                                | Stine et al.                           | 2 cross-sectional studies and 5 cohort studies | Biopsy and US                    | 23,059           | 3567      | OR             | 2.41 [1.27, 5.35]        | 0.009              | 95.0              |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |
|                                                     |                                         |                                     |                                  |                  |           |                |                          |                    |                   |

(Continued)
| Health outcomes | Author | Study design | NAFLD diagnosis | Participants | Type of metric | Effect size | 95% CI | p value | Heterogeneity | Small-study effect |
|----------------|--------|-------------|-----------------|--------------|----------------|-------------|--------|---------|--------------|-----------------|
| NAFLD diagnosis | Liu et al. | 6 case–control studies and 5 cohort studies | Biopsy, US, CT, and ICD code | NA | OR | 2.46 (1.77, 3.44) | 0.000* | 72.6 | 0.003 | 0.000 | 0.000* |
| NAFLD diagnosis | Liu et al. | 5 case–control studies and 4 cohort studies | Biopsy, US, CT, and ICD code | 458,582 | NA | OR | 2.24 (1.58, 3.17) | 0.000* | 68.4 | 0.023 | 0.407* |
| NAFLD diagnosis | Liu et al. | 5 case–control studies and 4 cohort studies | Biopsy, US, and ICD code | 224,822 | NA | OR | 1.49 (1.20, 1.84) | 0.000* | 83.5 | <0.001 | 0.945 |
| NAFLD diagnosis | Liu et al. | 5 case–control studies and 4 cohort studies | Biopsy and US | 1,217 | NA | OR | 1.21 (1.04, 1.41) | <0.0001 | 59.0 | 0.02 | 0.601* |
| Colorectal adenoma | Chen et al. | 8 cross-sectional studies and 4 cohort studies | Biopsy, US, and CT | 22,482 | NA | OR | 1.49 (1.20, 1.84) | 0.000* | 83.5 | 0.000 | 0.000 |
| Colorectal cancer | Liu et al. | 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* | 72.6 | 0.003 | 0.640* |
| Recurrent colorectal adenoma/cancer | Chen et al. | 4 cross-sectional studies and 5 cohort studies | Biopsy and US | 458,582 | NA | OR | 1.51 (1.44, 1.58) | <0.0001 | 59.0 | 0.02 | 0.601* |
| Right colon tumors | Lin et al. | 4 cross-sectional studies and 5 cohort studies | Biopsy, US, and ICD code | 8675 | 127 | OR | 1.41 (1.24, 1.59) | <0.0001 | 68.4 | 0.023 | 0.407* |
| Left colon tumors | Lin et al. | 5 cross-sectional studies and 5 cohort studies | Biopsy, US, CT, and ICD code | 7895 | 102 | OR | 1.45 (1.44, 1.59) | <0.0001 | 68.4 | 0.023 | 0.407* |
| Esophageal cancer | Mantovani et al. | 4 cross-sectional studies and 5 cohort studies | US and ICD code | 22,482 | NA | OR | 1.49 (1.20, 1.84) | 0.000* | 83.5 | 0.000 | 0.000 |
| Stomach cancer | Mantovani et al. | 4 cross-sectional studies and 5 cohort studies | Biopsy, US, and ICD code | 22,482 | NA | OR | 1.45 (1.44, 1.59) | <0.0001 | 59.0 | 0.02 | 0.601* |
| Pancreas cancer | Mantovani et al. | 4 cross-sectional studies and 5 cohort studies | Biopsy, US, and ICD code | 22,482 | NA | OR | 1.41 (1.24, 1.59) | <0.0001 | 59.0 | 0.02 | 0.601* |
| IP by means of 5-6 h L/M or L/R | De Munck et al. | 7 observational studies | Biopsy and US | 205 | 119 | SMD | 0.79 (0.49, 1.09) | 0.000* | 88.8 | 0.000 | 0.036* |
| IP by means of serum zonulin | De Munck et al. | 5 observational studies | Biopsy and US | 353 | 191 | SMD | 1.04 (0.40, 1.68) | 0.0001 | 86.0 | 0.02 | 0.601* |
| Gastroesophageal reflux disease | Xue et al. | 6 cross-sectional studies, 3 cohort studies, and 2 case–control studies | US and ICD code | 55,655 | 115 | OR | 1.41 (1.24, 1.59) | <0.0001 | 59.0 | 0.02 | 0.601* |
| Overall survival of AP | Váncsa et al. | 2 cross-sectional studies | US and ICD code | 74,678 | NA | OR | 1.28 (1.12, 1.44) | 0.000* | 83.5 | 0.000 | 0.000 |
| Moderately severe/severe AP | Váncsa et al. | 2 cross-sectional studies, 6 cohort studies, and 2 case–control studies | US and ICD code | 142,387 | 17,967 | OR | 1.28 (1.12, 1.44) | 0.000* | 83.5 | 0.000 | 0.000 |
| Colorectal polyps | Chen et al. | 12 cross-sectional studies, 6 cohort studies, and 2 case–control studies | Biopsy and US | 142,387 | 17,967 | OR | 1.28 (1.12, 1.44) | 0.000* | 83.5 | 0.000 | 0.000 |

Table 1. (Continued)
| Health outcomes                  | Author                      | Studies (n)                                                                 | NAFLD diagnosis                     | Participants (n) | Cases (n) | Type of metric | Effect size 95% CI | p value | Heterogeneity | Small-study effect | p value | p value |
|----------------------------------|-----------------------------|----------------------------------------------------------------------------|-------------------------------------|------------------|------------|----------------|-------------------|---------|---------------|---------------------|---------|---------|
| **Skeletal system disorders**    |                             |                                                                            |                                     |                  |            |                |                   |         |               |                     |         |         |
| Total BMD                        | Mantovani et al.            | 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.            | 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.            | 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.            | 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.            | 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.                | 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.                  | 6 cross-sectional studies and 1 cohort studies                            | Biopsy, US, FLL, HIS, LAL, 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.                  | 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.                  | 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.                  | 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.                  | 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.                  | 5 cohort studies                                                          | NR                                  | 465,112          | 6924       | HR             | 1.05 [0.89, 1.25]  | 0.562*  | 35.3          | 0.186               | 0.300*  |         |

(Continued)
| Health outcomes | Author | Studies (n) | NAFLD diagnosis | Participants | Type of metric | Effect size | 95% CI               | p value | Heterogeneity | p value | Small-study effect |
|----------------|--------|------------|-----------------|--------------|----------------|------------|---------------------|---------|---------------|---------|------------------|
| Hepatocellular carcinoma mortality | Liu et al. | 2 cohort studies | NR | 470,775 | 255 | HR | 2.53 (1.23, 5.18) | 0.000* | 81.2 | <0.01 | NA |
| ACM in OVD patients | Wu et al. | 5 cohort studies | Bopy, US, and liver enzyme | 21,186 | 3186 | HR | 1.14 (0.91, 1.32) | 0.076 | 65.4 | 0.08 | 0.109 |
| CVD mortality | Wu et al. | 5 cohort studies | Bopy, US, and liver enzyme | 2,800 | 1903 | HR | 1.01 (0.86, 1.14) | 0.40 | 64.9 | 0.02 | 0.378 |
| COVID-19 mortality | Singh et al. | 7042 | NR | 470,775 | 255 | HR | 2.53 (1.23, 5.18) | 0.000* | 81.2 | <0.01 | NA |
| ACM in female | Kläsi et al. | 1 cohort-study and liver enzyme | 10,877 | NA | OR | 1.65 (1.12, 2.34) | 0.012 | 98.7 | <0.01 | NA |
| Metabolic disorders | Mantovani et al. | 24 cohort-studies | US and CT | 4,895 | 2247 | HR | 2.19 (1.93, 2.48) | 0.000* | 91.2 | 0.000 | 0.05* |
| T2D mortality | Mantovani et al. | 24 cohort-studies | US and CT | 8,141 | 1,451 | HR | 1.41 (1.18, 1.68) | 0.000* | 93.3 | <0.001 | 0.014 |
| Metabolic syndrome | Balestri et al. | 12 cohort-studies and liver enzyme | 10,877 | NA | OR | 1.65 (1.12, 2.34) | 0.000 | 98.7 | <0.01 | NA |
| Metabolic syndrome in T2D | Balestri et al. | 9 cohort-studies | US | 1,710 | 261 | OR | 1.84 (1.51, 1.89) | 0.000 | 96.0 | <0.0001 | 0.005 |
| Metabolic syndrome in T2D | Song et al. | 7 cohort-studies and liver enzyme | US and CT | 236,400 | NA | OR | 1.84 (1.51, 1.89) | 0.000 | 96.0 | <0.0001 | 0.005 |
| Diabetic retinopathy in T2D | Song et al. | 9 cohort-studies | US | 7170 | 261 | OR | 1.90 (1.54, 2.36) | 0.000 | 96.0 | <0.0001 | 0.005 |
| Urinary system cancers | Ballestri et al. | 4 cohort-studies | US and ICD-code | 120,851 | 414 | HR | 1.30 (1.04, 1.67) | 0.025* | 10.4 | 0.35 | 0.37 |
| Urinary system cancers | Ballestri et al. | 12 longitudinal studies | Bopy, US, and liver enzyme | 26,680 | 2141 | HR | 1.79 (1.16, 2.65) | 0.000 | 93.0 | <0.01 | 0.01 |
| Nephrological disorders | Musso et al. | 16 cross-sectional studies | US | 27,012 | 2694 | OR | 2.12 (1.61, 2.86) | <0.001* | 77.0 | <0.0001 | 0.47 |
| Incident CKD | Musso et al. | 12 longitudinal studies | Bopy, US, and liver enzyme | 26,830 | 2141 | HR | 1.79 (1.16, 2.65) | 0.000 | 93.0 | <0.01 | 0.01 |
| Albuminuria | Wijarnpreecha et al. | 17 cross-sectional studies and 2 cohort-studies | US, FLI, and transient elastography | 2,880 | NA | OR | 1.57 (1.12, 2.11) | 0.000 | 81.2 | <0.01 | NA |
### 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        | p value             |
| Serum marker disorders         |                               |             |                 |                  |          |                | p value     | I²             |                     |
| 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      | 0.412 [0.286, 0.938] | 0.000       | 77.6          | <0.0001            | 0.98                |
| Circulating leptin             | Polyzos et al. [39]           | 24 cross-sectional studies | Biopsy 2006    | 775              | SMD      | 0.44 [0.42, 0.84]   | <0.0001     | 85.7          | 0.000               | 0.344               |
| Serum ferritin                 | Du et al. [43]                | 3 case–control studies | Biopsy and US 225  | 101             | SMD      | 1.01 [0.89, 1.13]   | <0.0001     | 98.0          | <0.00001            | 0.0023*             |
| C-reactive protein             | Liu et al. [37,38]            | 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       | 3.36 [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    |                               |             |                 |                  |          |                | p value     | I²             |                     |
| Predicted FEV1                 | Mantovani et al. [56,59,60]   | 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. [56,59,60]   | 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          |                               |             |                 |                  |          |                | p value     | I²             |                     |
| 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)
| Health outcomes         | Author                      | Studies [n]                  | NAFLD diagnosis | Participants [n] | Cases [n] | Type of metric | Effect size          | Heterogeneity | Small-study effect |
|-------------------------|-----------------------------|-----------------------------|-----------------|------------------|-----------|----------------|----------------------|---------------|-------------------|
| Depression              | Xiao et al.                | 4 cohort studies            | NR              | 38,047           | 3305      | OR             | 1.29 [1.02, 1.64]   | 73.0          | 0.01              | 0.420*           |
| Endothelial dysfunction | Fan et al.                 | 2 cross-sectional studies   | Biopsy and US   | 906              | 545       | WMD            | -4.82 [-5.63, -4.00] | 57.5          | 0.009             | 0.188            |
| Carotid–femoral PWV     | Jaruvongvanich et al.      | 6 cross-sectional studies   | Biopsy, US, and CT | 3957          | 783       | MD             | 0.75 [0.37, 1.12]   | 89.0          | <0.01             | 0.013            |
| Brachial–ankle PWV      | Jaruvongvanich et al.      | 8 cross-sectional studies   | Biopsy, US, and CT | NA           | NA        | MD             | 0.82 [0.57, 1.07]   | 92.0          | <0.01             | 0.97             |
| Augmentation index      | Jaruvongvanich et al.      | 5 cross-sectional studies   | Biopsy, US, and CT | 12509         | 3334      | MD             | 2.54 [0.07, 5.01]   | 73.0          | 0.01              | 0.11             |
| Breast cancer           | Mantovani et al.           | 4 cohort studies            | US and ICD code | 85,827         | 1347      | HR             | 1.39 [1.13, 1.71]   | 95.0          | 0.002*            | 0.531*           |
| Thyroid cancer          | Mantovani et al.           | 2 cohort studies            | US and ICD code | 64,732         | 776       | HR             | 2.63 [1.27, 5.45]   | 6.3           | 0.07              | 0.72             |
| Female genital organ cancers | Mantovani et al.         | 4 cohort studies            | US and ICD code | 85,827         | 558       | HR             | 1.62 [1.13, 2.32]   | 40.8          | 0.15              | 0.296*           |
| Prostate cancer         | Mantovani et al.           | 5 cohort studies            | US and ICD code | 140,014        | 1002      | HR             | 1.16 [0.82, 1.64]   | 62.5          | 0.032             | 0.142*           |
| Hematological cancers   | Mantovani et al.           | 2 cohort studies            | US and ICD code | NA            | NA        | HR             | 1.47 [0.69, 3.12]   | NA            | 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 kidney 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.
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 fields and the quality of methodology of each publication, including in the current review. We found that NAFLD 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 NAFLD 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. Through early detection and intervention, subclinical atherosclerosis can be controlled and even reversed. 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       | Y         | N         | Y         | Y         | Y         | Y         | Y         | Critically low |
| Zhou et al.54               | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | Y         | Y         | Y         | Y         | Critically low |
| Ampuero et al.31            | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | Y         | N         | Critically low |
| Jaruvongvanich et al.17     | Y                  | Y                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | Y         | Y         | Critically low |
| Targher et al.41            | Y                  | Y                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | Y         | Y         | Critically low |
| Wu et al.42                 | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | Y         | N         | Y         | Y         | Critically low |
| Veracruz et al.91           | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | Y         | Y         | Critically low |
| Borges-Canha et al.59       | Y                  | N                          | Y         | PY       | Y         | Y         | Y         | PY       | Y         | N         | Y         | Y         | Y         | Y         | Critically low |
| Bonci et al.52              | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | N         | Y         | Y         | Critically low |
| Oikonomidou et al.78        | Y                  | Y                          | Y         | Y         | Y         | Y         | PY       | Y         | N         | Y         | 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         | Critically low |
| Wijarnpreecha et al.71      | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | Y         | Y         | Critically low |
| Cai et al.63,64             | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | Y         | Y         | Critically low |
| Liu et al.57,58             | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | N         | Y         | Critically low |
| Yao et al.48                | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | N         | Y         | Y         | Critically low |
| Mantovani et al.74,77       | Y                  | Y                          | Y         | PY       | Y         | Y         | Y         | Y         | Y         | Y         | Y         | Y         | Y         | Y         | Low |
| Ballestri et al.54          | Y                  | N                          | Y         | PY       | Y         | Y         | Y         | Y         | N         | N         | Y         | N         | Y         | Y         | Critically low |
| Song et al.50               | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | Y         | Y         | Y         | Y         | Critically low |
| Qin and Ding50              | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | N         | Y         | Critically low |
| Wongjarupong et al.47       | Y                  | Y                          | Y         | Y         | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | Y         | Y         | Low |
| Stine et al.50              | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | Y         | Y         | Y         | Critically low |
| Liu et al., 2021            | Y                  | N                          | Y         | PY       | Y         | Y         | PY       | Y         | N         | Y         | N         | N         | N         | N         | Critically low |
| References | AMSTAR 2 checklist | Overall assessment quality |
|------------|-------------------|--------------------------|
| Chen et al. | Y N Y Y Y Y N Y Y Y Y Y Y | Critically low |
| Munck et al. | Y N Y Y Y Y N Y Y Y Y Y Y | Critically low |
| Lin et al. | Y Y Y Y Y Y Y Y Y Y Y Y | Critically low |
| Xue et al. | Y N Y Y Y Y Y N Y Y Y Y Y Y | Critically low |
| Váncsa et al. | Y Y Y Y Y Y Y Y Y Y Y | Critically low |
| Chen et al. | Y Y Y Y Y N Y Y Y Y Y Y | Critically low |
| Musso et al. | Y Y Y Y Y Y Y Y Y Y Y Y | Low |
| Wijarnpreecha et al. | Y N Y Y Y Y Y Y Y Y Y Y Y | Critically low |
| Wijarnpreecha et al. | Y N Y Y Y Y Y Y Y Y Y Y Y | Critically low |
| Mantovani et al. | Y Y Y Y Y Y Y Y Y Y Y Y | Low |
| Upala et al. | Y Y Y Y N Y Y Y Y Y Y Y | Critically low |
| Cai et al., 2019 | Y N Y Y Y Y Y N Y Y Y Y Y Y | Critically low |
| Sun et al. | Y N Y Y N Y Y Y Y Y Y N Y | Critically low |
| Fan et al. | Y N Y Y Y Y Y N Y N N Y Y Y Y | Critically low |
| Januvongvanich et al. | Y Y Y Y Y Y Y Y Y Y Y Y | Low |
| Hu et al. | Y N Y Y N Y Y N Y N Y Y Y Y | Critically low |
| Mahfood Haddad et al. | Y N Y Y N Y Y Y Y N Y Y Y Y | Critically low |
| Liu et al. | Y N Y Y Y Y Y Y Y Y Y Y Y | Critically low |
| Singh et al. | Y N Y Y Y Y Y N Y Y Y Y | Critically low |
| Khalid et al. | Y N Y Y Y Y Y N Y N Y Y Y Y | Critically low |
| Dai et al. | Y N Y Y Y Y Y N Y Y Y Y | Critically low |
| Madan et al. | Y N N Y Y Y N N N Y Y | Critically low |
| References          | AMSTAR 2 checklist | Overall assessment quality |
|---------------------|--------------------|----------------------------|
| Polyzos et al.      | Y N Y PY Y Y PY Y N Y Y Y Y Y           | Critically low             |
| Du et al.           | Y N Y PY Y PY PY Y N Y Y Y N Y           | Critically low             |
| Liu et al.          | Y N Y PY Y PY PY Y N Y Y Y N N           | Critically low             |
| Han et al.          | Y N Y PY Y PY PY Y N Y Y Y N Y           | Critically low             |
| Mantovani et al.    | Y Y Y PY Y Y Y Y Y Y Y N Y Y            | Low                        |
| Ismaiel et al.      | Y N Y PY Y Y Y Y N Y N Y Y Y Y           | Critically low             |
| Eliades et al.      | Y N Y PY Y PY PY Y N Y N N Y Y           | Critically low             |
| Mantovani et al.    | Y Y Y PY Y Y Y Y Y N Y N Y N N           | Low                        |
| Hegyi et al.        | Y Y Y PY Y Y Y Y N Y N Y Y Y N           | Critically low             |
| Xiao et al.         | Y N Y PY Y Y PY Y N N Y Y Y Y N           | 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 described 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.
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, 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. 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. In addition to insulin resistance, pro-inflammatory factors, oxidative stress, the ren-angiotensin-aldosterone system also plays a role in the pathogenesis.

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 (e.g. 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. But the prevalence of NAFLD is equal in men and post-menopausal women. 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 | P < 50% and Cochran Q-test p > 0.1 |                               |       |
| Cardiovascular disorders             |                  |                           |                        |                                             |       |
| C-IMT in adult patients               | Madan et al.33    | Yes                       | Yes                    | Yes                                         | High  |
| C-IMT in adult patients               | Madan et al.33    | Yes                       | No                     | Yes                                         | Weak  |
| C-IMT in pediatric patients           | Madan et al.33    | No                        | No                     | Yes                                         | Weak  |
| CAC                                   | Zhou et al.54     | Yes                       | Yes                    | No                                          | Weak  |
| Arterial stiffness                    | Zhou et al.54     | Yes                       | Yes                    | No                                          | Weak  |
| Endothelial dysfunction               | Zhou et al.54     | No                        | No                     | No                                          | Weak  |
| Subclinical atherosclerosis           | Ampuero et al.31  | No                        | Yes                    | Yes                                         | Moderate |
| CAC score > 0                         | Jaruvongvanich et al.37| No                       | Yes                    | No                                          | Weak  |
| CAC score > 100                       | Jaruvongvanich et al.37| No                       | No (p > 0.05)          | Yes                                         | NA    |
| Fatal CVD                             | Targher et al.41  | Yes                       | No (p > 0.05)          | No                                          | NA    |
| Fatal and non-fatal CVD               | Targher et al.41  | Yes                       | No                     | Yes                                         | NA    |
| Non-fatal CVD                         | Targher et al.41  | No                        | Yes                    | Yes                                         | NA    |
| CAD                                   | Wu et al.52       | No                        | No                     | Yes                                         | Weak  |
| CVD                                   | Veracruz et al.81 | Yes                       | Yes                    | Yes                                         | NA    |
| LVEF                                  | Borges-Canha et al.55| Yes              | No (p > 0.05)          | Yes                                         | NA    |
| Peak E velocity                       | Borges-Canha et al.55| Yes              | No (p > 0.05)          | No                                          | NA    |
| E/e' ratio                            | Borges-Canha et al.55| Yes              | Yes                    | No                                          | Weak  |
| Peak A velocity                       | Borges-Canha et al.55| Yes              | Yes                    | Yes                                         | NA    |
| E/A ratio                             | Borges-Canha et al.55| Yes              | Yes                    | Yes                                         | NA    |
| Isovolumic relaxation time            | Borges-Canha et al.55| No               | No                     | No                                          | Weak  |
| Deceleration time                     | Borges-Canha et al.55| Yes              | Yes                    | No                                          | Weak  |

(Continued)
| Health outcomes                          | Author, year       | Precision of the estimate | Consistency of results | No evidence of small-study effects (P>0.1) | Grade |
|-----------------------------------------|--------------------|---------------------------|------------------------|------------------------------------------|-------|
| Left ventricle mass                    | Borges-Canha et al. | Yes                       | Yes                    | No                                       | No    |
| Left ventricle end-diastolic diameter  | Borges-Canha et al. | Yes                       | Yes                    | Yes                                      | High  |
| Left ventricle end-systolic diameter   | Borges-Canha et al. | Yes                       | No [p > 0.05]          | Yes                                      | NA    |
| Left atrium diameter                   | Borges-Canha et al. | Yes                       | Yes                    | Yes                                      | Moderate|
| Posterior wall thickness               | Borges-Canha et al. | Yes                       | No                     | Yes                                      | Moderate|
| Interventricular septum thickness      | Borges-Canha et al. | Yes                       | Yes                    | Yes                                      | Moderate|
| LV mass indexed to BSA                 | Bonci et al.       | No                        | Yes                    | No                                       | Weak  |
| LV mass indexed to height              | Bonci et al.       | No                        | No [p > 0.05]          | Yes                                      | NA    |
| EFT thickness                          | Oikonomidou et al. | No                        | Yes                    | No                                       | Weak  |
| GLS                                     | Oikonomidou et al. | No                        | Yes                    | Yes                                      | Weak  |
| Diastolic cardiac dysfunction          | Wijarnpreecha et al. | No                        | Yes                    | No                                       | Weak  |
| Cardiac conduction defect              | Wijarnpreecha et al. | No                        | No                     | No                                       | Weak  |
| Atrial fibrillation                    | Cai et al.         | Yes                       | No                     | Yes                                      | Weak  |
| Epicardial adipose tissue              | Liu et al.         | Yes                       | Yes                    | No                                       | Weak  |
| Hypertension and prehypertension       | Yao et al.         | No                        | Yes                    | No                                       | Weak  |
| Cerebral and cerebrovascular disease   |                    |                           |                        |                                          |       |
| Cerebrovascular accident                | Hu et al.          | No                        | Yes                    | Yes                                      | Moderate|
| Ischemic stroke                        | Hu et al.          | No                        | Yes                    | No                                       | Weak  |
| Cerebral hemorrhage                    | Hu et al.          | No                        | No                     | Yes                                      | Weak  |
| Stroke and cerebrovascular diseases    | Veracruz et al.    | Yes                       | Yes                    | No                                       | Weak  |
| Health outcomes                      | Author, year        | Precision of the estimate | Consistency of results | No evidence of small-study effects (P > 0.1) | Grade |
|--------------------------------------|---------------------|---------------------------|------------------------|---------------------------------------------|-------|
|                                     |                     | > 1000 disease cases      | 1000 disease cases     |                                             |       |
|                                     |                     | p < 0.001                 | p < 0.001              |                                             |       |
| Stroke                               | Mahfood Haddad et al.\(^{64}\) | No                        | Yes                    | Yes                                         | Moderate |
| Digestive disorder                  |                     |                           |                        |                                             |       |
| Gallstone disease                    | Qin and Ding\(^{40}\) | Yes                       | No                     | No                                          | Weak   |
| Cholangiocarcinoma                   | Wongjarupong et al\(^{47}\) | Yes                       | Yes                    | No                                          | Moderate |
| HCC with/without cirrhosis           | Stine et al\(^{50}\) | Yes                       | No [p > 0.05]           | No                                          | NA     |
| HCC without cirrhosis                | Stine et al\(^{50}\) | Yes                       | No                     | No                                          | Weak   |
| ICC                                  | Liu et al., 2021    | No                        | Yes                    | No                                          | Weak   |
| ECC                                  | Liu et al., 2021    | No                        | Yes                    | No                                          | Weak   |
| Colorectal adenoma                   | Chen et al.\(^{56}\) | No                        | No                     | Yes                                         | Weak   |
| Colorectal cancer                    | Liu et al., 2021    | No                        | Yes                    | No                                          | Weak   |
| Recurrent colorectal adenoma/cancer  | Chen et al.\(^{56}\) | No                        | No                     | Yes                                         | Weak   |
| Right colon tumors                   | Lin et al.\(^{75}\) | Yes                       | Yes                    | Yes                                         | Moderate |
| Left colon tumors                    | Lin et al.\(^{75}\) | Yes                       | Yes                    | No                                          | Moderate |
| Esophagus cancer                     | Mantovani et al\(^{74,77}\) | No                        | No                     | Yes                                         | Weak   |
| Stomach cancer                       | Mantovani et al\(^{74,77}\) | No                        | No                     | No                                          | Weak   |
| Pancreas cancer                      | Mantovani et al\(^{74,77}\) | No                        | No                     | Yes                                         | Weak   |
| IP by means of 5-6 h L/M or L/R      | Munck et al.\(^{66}\) | No                        | Yes                    | Yes                                         | Moderate |
| IP by means of serum zonulin         | Mu Munck et al., 2020 | No                        | Yes                    | No                                          | Weak   |
| Gastroesophageal reflux disease      | Xue et al\(^{62}\)  | No                        | Yes                    | No                                          | Weak   |
| Overall survival of AP               | Váncsa et al.\(^{70}\) | No                        | No [p > 0.05]           | No                                          | NA     |
| Moderately severe/severe AP          | Váncsa et al.\(^{70}\) | No                        | No                     | No                                          | Weak   |
| Colorectal polyps                    | Chen et al.\(^{65}\) | Yes                       | Yes                    | No                                          | Weak   |
| Health outcomes | Author, year | Precision of the estimate | Consistency of results | No evidence of small-study effects (P > 0.1) | Grade |
|-----------------|-------------|---------------------------|------------------------|--------------------------------------------|-------|
| **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. 62 | Yes | No (p > 0.05) | No | Yes | NA |
| CVD mortality | Wu et al. 62 | 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 |
| Health outcomes                      | Author, year         | Precision of the estimate | Consistency of results | No evidence of small-study effects (P > 0.1) | Grade  |
|-------------------------------------|----------------------|---------------------------|------------------------|---------------------------------------------|--------|
|                                     |                      |                           |                        |                                             |        |
| Diabetic retinopathy in T2D         | Song et al.          | Yes                       | No [p > 0.05]          | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | NA     |
| Urological disorder                 |                      |                           |                        |                                             |        |
| Urolithiasis                        | Wijarnpreecha et al. | No                        | Yes                    | Yes                                         | Yes    |
|                                     |                      |                           |                        |                                             | Moderate|
| Urinary system cancers              | Mantovani et al.     | No                        | No                     | Yes                                         | Yes    |
|                                     |                      |                           |                        |                                             | Weak   |
| Nephrological                       |                      |                           |                        |                                             |        |
| Prevalent CKD                       | Musso et al.         | Yes                       | Yes                    | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | Moderate|
| Incident CKD                        | Musso et al.         | Yes                       | Yes                    | Yes                                         | Yes    |
|                                     |                      |                           |                        |                                             | High   |
| Albuminuria                         | Wijarnpreecha et al. | No                        | Yes                    | No                                          | No     |
|                                     |                      |                           |                        |                                             | Weak   |
| Serum marker disorders              |                      |                           |                        |                                             |        |
| Homocysteine level                  | Dai et al.           | No                        | Yes                    | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | Weak   |
| Folate level                        | Dai et al.           | No                        | No [p > 0.05]          | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | NA     |
| Vitamin B12                         | Dai et al.           | No                        | No [p > 0.05]          | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | NA     |
| MPV                                 | Madan et al.         | No                        | Yes                    | Yes                                         | Yes    |
|                                     |                      |                           |                        |                                             | Moderate|
| Circulating leptin                  | Polyzos et al.       | No                        | Yes                    | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | Weak   |
| Serum ferritin                      | Du et al.            | No                        | Yes                    | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | Weak   |
| C-reactive protein, CRP             | Liu et al.           | Yes                       | Yes                    | No                                          | No     |
|                                     |                      |                           |                        |                                             | Weak   |
| Serum resistin level                | Han et al.           | Yes                       | No                     | No                                          | No     |
|                                     |                      |                           |                        |                                             | Weak   |
| Visfatin Levels                     | Ismaiel et al.       | No                        | No [p > 0.05]          | No                                          | No     |
|                                     |                      |                           |                        |                                             | NA     |
| vitamin D deficiency                | Eliades et al.       | Yes                       | Yes                    | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | Moderate|
| Respiratory system disorder         |                      |                           |                        |                                             |        |
| Predicted FEV1                       | Mantovani et al.     | Yes                       | Yes                    | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | Moderate|
| Predicted FVC                        | Mantovani et al.     | Yes                       | Yes                    | No                                          | Yes    |
|                                     |                      |                           |                        |                                             | Moderate|
### Table 3. (Continued)

| Health outcomes                | Author, year | Precision of the estimate | Consistency of results | No evidence of small-study effects ($P > 0.1$) | Grade |
|-------------------------------|--------------|---------------------------|------------------------|----------------------------------------------|-------|
| Lung cancer                   | Mantovani et al.76,77 | No                        | Yes                    | Yes                                          | Moderate |
| Other health outcomes         |              |                           |                        |                                              |       |
| Severe COVID-19               | Hegyi et al.73 | No                        | No                     | No                                           | Weak  |
| ICU admission of COVID-19     | Hegyi et al.73 | No                        | No ($p > 0.05$)         | No                                           | NA    |
| Depression                    | Xiao et al.82 | Yes                       | No                     | Yes                                          | Weak  |
| Endothelial dysfunction       | Fan et al.36  | No                        | Yes                    | No                                           | Weak  |
| Carotid–femoral PWV           | Jaruvongvanich et al.27 | No                      | Yes                    | No                                           | Weak  |
| Brachial–ankle PWV            | Jaruvongvanich et al.27 | No                      | Yes                    | No                                           | Weak  |
| Augmentation index            | Jaruvongvanich et al.27 | Yes                      | No                     | Yes                                          | Weak  |
| Breast cancer                 | Mantovani et al.76,77 | Yes                      | No                     | Yes                                          | Weak  |
| Thyroid cancer                | Mantovani et al.76,77 | No                        | No                     | Yes                                          | Weak  |
| Female genital organ cancers  | Mantovani et al.76,77 | No                        | No                     | Yes                                          | Weak  |
| Prostate cancer               | Mantovani et al.76,77 | Yes                       | No ($p > 0.05$)         | No                                           | Weak  |
| Hematological cancers         | Mantovani et al.76,77 | NO                        | NO ($p > 0.05$)         | 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; EF, 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.
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. 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.

Acknowledgements
The authors would like to acknowledge all authors of the original studies that were included in this meta-analysis.

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Lixian Zhong: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.
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Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Consent statement and ethical approval
Consent statement and ethical approval are not required as the current study does not involve human participants and animal subjects.

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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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