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Review Article

Exploring the link between non-alcoholic fatty liver disease and depression: a systematic review and meta-analysis of bidirectional risk

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Abstract: Objective: This study aims to consolidate evidence regarding the occurrence of depression among non-alcoholic fatty liver disease (NAFLD) patients and explore the bidirectional relationship between NAFLD and depression. Methods: Three major databases: Medline, Google Scholar, and ScienceDirect, were searched for relevant studies published up to August 2023 that report the incidence of depression in patients with NAFLD and investigate a correlation between NAFLD and depression. The quality of the studies was evaluated using the Joanna Briggs Institute checklist. The final pooled prevalence was reported with a 95% confidence interval (CI), and the pooled incidence of depression among NAFLD patients was summarized as a pooled Odds ratios (OR) with a 95% CI. Results: A total of 16 studies were included in the analysis. The pooled prevalence of depression (15 studies) among NAFLD patients was 19% (95% CI: 16%-22%) (*P*-value < 0.001). Patients with NAFLD had a 28%-increased risk (OR 1.28, 95% CI: 1.06-1.55, *P*-value < 0.001) of developing depression compared to non-NAFLD patients (10 studies). Conversely, patients with depression had 2.32 times higher odds (OR 2.32, 95% CI: 1.13-4.78, *P*-value 0.03) of developing NAFLD (two studies). Subgroup analyses based on sample size and geographic region revealed variations in prevalence estimates. Conclusion: Robust evidence supported a bidirectional link between NAFLD and depression. These findings underscore the importance of comprehensive patient care strategies that encompass both physical and mental well-being.

Keywords: Non-alcoholic fatty liver disease, NAFLD, depression, systematic review, meta-analysis

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently on the rise, with a 25% estimated global incidence rate [1, 2]. Recent studies reported an association between NAFLD and depression, revealing intriguing connections between these seemingly distinct diseases [3]. Depression is currently the third most common cause of disability worldwide [4], and is often associated with lower quality of life, disability, and increased mortality [4, 5]. Several studies showed that depression coexists with other disorders, such as metabolic syndrome (MS), diabetes mellitus (DM), and obesity, and may significantly effect health outcomes [6, 7].

Studies show that the shared pathophysiologic mechanisms of NAFLD and depression may include systemic inflammation, oxidative stress, insulin resistance, and gut dysbiosis that contribute to the bidirectional nature of this association [8, 9]. Chronic low-grade inflammation and insulin resistance play a pivotal role in both conditions, contributing to hepatic steatosis and neuroinflammation, which in turn may exacerbate depressive symptoms. Additionally, individuals with NAFLD often exhibit poor dietary habits, physical inactivity, and sleep disturbance, all of which are known risk factors for depression. Conversely, depression itself may contribute to the onset or worsening of NAFLD by promoting stress-related metabolic changes and increasing the likelihood of weight gain and unhealthy behaviors [10]. Recent studies have established that in patients, depression is associated with a 2-fold higher risk of developing MS and DM. However, the link between depression and NAFLD, as well as the

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bidirectional relationship between these conditions, remains unclear [11-14]. The previous two meta-analyses by Xiao et al. (2021) [15] and Gu et al. (2022) [16] included only ten and seven studies, respectively. This review and meta-analysis aim to summarize all current data, and comprehensively analyze the occurrence of depression among NAFLD patients to explore the bidirectional relationship between these diseases.

Materials and methods

Research questions

1. What is the incidence rate of depression among patients diagnosed with NAFLD?

2. What is the connection between depression and NAFLD and vice versa?

Methods

Study results were reported in adherence to the 2020 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Supplementary Table 1) [17]. Ethical approval was not applicable since the review included literature freely available across various databases. The protocol was prioritized and registered at PROSPERO, CRD42023457671.

Study selection and eligibility criteria

A systematic electronic search of the Medline, Google Scholar, and ScienceDirect databases was conducted from inception to August 2023 for studies published in English. All descriptive and analytical studies (cross-sectional, cohort, and case-control) that reported the occurrence of depression in patients diagnosed with NAFLD were included. Articles that were not peer-reviewed, unpublished theses, clinical trials, conference abstracts, and narrative reviews were excluded. Additionally, studies that did not report primary outcomes (incidence of depression among NAFLD patients) lacked data on NAFLD diagnosis (e.g., missing histology or imaging confirmation), or reported data on children were excluded.

The information on the incidence of depression was extracted, and the risk of NALFD in patients with and without depression (any form) was compared. Relevant data were extracted and pooled into Forrest plots.

Definitions

Definition of NAFDL: NAFLD was diagnosed by imaging or histologic evidence suggestive of excess hepatic fat in liver parenchyma, absence of secondary causes of increased hepatic fat, and no history of recent or ongoing alcohol consumption [18]. Since different studies employed varying definitions for NAFLD based on clinical, histologic, and imaging criteria, the review considered all studies that reported NAFLD diagnosis per the criteria of the primary authors (diagnosed using either serum-based criteria, imaging, or histology/biopsy).

Definition of depression: The diagnosis of depression was divided into three categories, in line with a previous article: self-rated, self-reported, and clinician-rated [19]. Self-rated diagnosis of depression is based on responses to the Patient Health Questionnaire-9 (PHQ-9), Hospital Anxiety and Depression Scale (HADS), Korean Center for Epidemiological Studies-Depression Scale (CES-D), and Beck's Depression Inventory (BDI). Self-reported diagnosis included the identification of depression through self-reporting of medical history and intake of medications for depression. A clinician-rated diagnosis is based on the diagnosis of depression by a psychiatrist using the criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), and the International Classification of Disease, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes. The analysis did not include studies on children.

Outcome criteria

Occurrence of depression in NAFLD patients was the primary outcome. Pooled risk of depression among NAFLD and non-NAFLD patients were obtained from studies that reported depression as the exposure of interest. The risk of developing NAFLD among depressed and non-depressed individuals was also obtained. Outcomes were stratified by age and gender.

Search strategy

Medical subject heading (MeSH) terms such as: "Depression" OR "Depressed" OR "depress*.tw". AND "NAFLD" AND "Non-alcoholic fatty liver disease" AND "Hepatic steatosis" AND "Fatty steatosis" AND "Observational stud-

ies" OR "Descriptive studies" OR "Prospective studies" were used to search the 3 included databases. Cross references of the included studies were also searched. The detailed search strategy is summarized in the Supplementary Appendix.

Data collection and analysis

Selection of studies: Two primary researchers (LM and HY) independently screened the titles and abstracts of the identified studies and subsequently extracted the relevant full texts. All necessary details for the systematic review and subgroup analyses were extracted from the individual articles.

Data extraction and management: Relevant information, including the authors' details, study design and region, eligibility criteria, definition of NAFLD and depression, and sample size, was extracted and entered into the data documentation sheet.

Statistical analysis

The extracted data were analyzed using STATA 14.2. For each study, the standard error was calculated using the reported prevalence and sample size. The "metaprop" function was used to perform a prevalence meta-analysis [20]. The Freeman-Tukey double arc-sine transformation was used to mitigate the effects of large and small studies on the pooled estimates. The final pooled prevalence was reported along with a 95% confidence interval (CI). The pooled incidence of depression among NAFLD was summarized using the Mantel-Haenszel method as a pooled Odds ratio (OR) with a 95% confidence interval (CI). Subgroup analysis was done based on sample size and the study location. Publication bias assessment was performed using a funnel plot and Egger's test [21]. The sensitivity analysis was done to understand the impact of the quality of included studies on the pooled estimates.

Assessment of heterogeneity

The between-study variation was evaluated using the I^2 statistic and the Chi-square heterogeneity test. Heterogeneity was categorized into three groups: mild (I^2 25%), moderate (I^2 25-75%), and substantial (I^2 > 75%). The pooled prevalence and publication bias were represented graphically using a Forrest plot and a funnel plot.

Quality of included studies

Joanna Briggs Institute (JBI) Critical Appraisal Tool [22] was used to assess study quality. The tool is commonly utilized to evaluate observational studies in prevalence meta-analyses. It rates studies based on the appropriateness of sample frame, data analysis, sample size, sampling method, statistical analysis, methods, and response rate competence.

Results

Study selection

A database search identified 3556 articles. Of them, 1151 were removed as duplicates. Additional 1971 articles were removed after the title and abstract screening. Of the remaining 434 papers, 43 full-text articles were retrieved. Of these, 31 studies had different study participants (n = 27) and were published in languages other than English (n = 4); therefore, they were excluded. Thirteen studies reported a mixed study population, including patients with hepatitis, hepatocellular carcinoma cases, and NALFD. Fourteen studies had estimated other psychiatric illnesses other than depression, such as anxiety and stress. Finally, 16 articles were deemed eligible for the meta-analysis [11-14, 23-34]. Fifteen articles [11-14, 23-26, 28-34] estimated the pooled incidence of depression among NAFLD patients, ten articles [12-14, 23-26, 28-30] reported the risk of development of depression in NAFLD patients, and two articles [12, 27] reported the risk of NAFLD among patients with and without depression. The flow diagram of the search strategy is shown in **Figure 1**.

Characteristics of the included studies

As shown in **Table 1**, eight out of 16 included studies were from the American continent, six from Asia, and two from Europe. All studies were retrospective and reported results in English. Studies included between 184 and 1980950 patients. In eight studies, the diagnosis of NAFLD was based on histology. In eight studies, depression was diagnosed by various questionnaires.

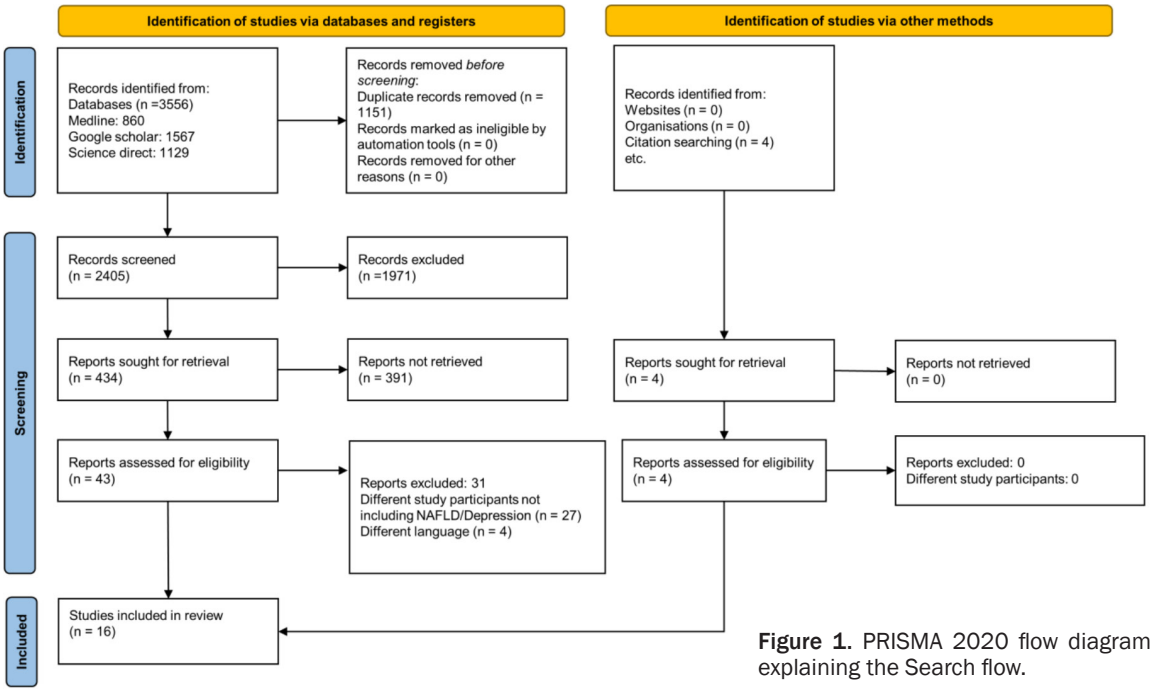

Figure 1. PRISMA 2020 flow diagram explaining the Search flow.

Burden of depression among NALFD patients

Fifteen studies with 2,055,007 participants reported on the depression prevalence in NALFD patients [11-14, 23-26, 28-34]. The pooled estimates (**Figure 2**) were calculated after adjusting for population weights. The overall pooled prevalence of depression among NALFD patients with NAFLD was 19% (95% CI 16%-22%). A subgroup analysis based on the sample size and the region showed that the prevalence was higher in studies with the number of patients less than 10,000 [pooled prevalence 24% (95% CI 18%-30%)] (Supplementary Figure 1) and in studies conducted in North America [pooled prevalence 25% (95% CI 18%-32%)] (Supplementary Figure 2).

Incidence of depression among patients with non-alcoholic fatty liver disease

Ten articles (n = 306292; NAFLD = 72827, non NAFLD = 233465) reported the incidence of depression in NAFLD patients [12-14, 23-26, 28-30]. Patients with NAFLD had 1.28 times higher odds of developing depression when compared to individuals with no NAFLD (pooled OR of 1.28, 95% CI: 1.06-1.55, with high heterogeneity I^2 = 96.8, *P*-value < 0.001) (**Figure 3**). Subgroup analysis based on sample size and region revealed that the increased risk remained significant for studies reported outside Asia (Supplementary Figure 3) and for studies with smaller sample sizes (Supplementary Figure 4). Two studies reported on the risk of depression among patients with NAFLD, separately for men and women. However, our pooled estimates revealed no significant gender-associated risk (Supplementary Figures 5 and 6). The adjusted odds (aOR) of depression among patients with NAFLD, as compared to patients without NAFLD, were pooled. Based on the ten studies, patients with NAFLD had 1.39 times higher odds of developing depression when compared to patients with no NAFLD after adjusting for potential confounders (pooled OR of 1.39, 95% CI: 1.21-1.60, with high heterogeneity I^2 = 80.9, *P*-value < 0.001) (Supplementary Figure 7).

Rate of non-alcoholic fatty liver disease and depression

Only two articles reported on the risk of development of NALFD in patients with and without depression [12, 27]. The pooled estimates showed that patients with depression have 2.32 times higher chances of developing NAFLD when compared to patients with no depression (pooled OR of 2.32, 95% CI: 1.13-4.78, with high heterogeneity I^2 = 78.8%, *P*-value 0.03) (**Figure 4**). A subgroup analysis

Table 1. Characteristics of included studies, n = 16

Author, year	Country	Sample Size	Study type	NAFLD definition	Inclusion and Exclusion criteria	Age (median and range/ Mean (SD))	Depression definition	Summary of findings	Quality of study (JBI)
Choi 2021 [23]	Korea	25333 (NAFLD = 7846, Non NAFLD = 17487)	Retrospective cross-sectional	Hepatic ultrasonography was performed to diagnose fatty liver by experienced radiologists	The subjects (age ≥ 20 years) voluntarily attended a general health check-up, underwent examinations including abdominal ultrasonography and blood samplings and completed a symptom questionnaire	49.40 (10.04)	The depression status was evaluated using the Beck Depression Inventory (BDI) scale	The prevalence rate of NAFLD was noted to be 30.9%. In the multivariate analysis, NAFLD showed a significant association with depression [aOR 1.43, 95% CI 1.14-1.80, *P* = 0.002] in women. Severe NAFLD significantly correlated with state anxiety (aOR 1.84, 95% CI 1.01-3.37, *P* = 0.047) in women.	Low
Labenz 2020 [14]	Germany	39742 (NAFLD = 19871, Non NAFLD = 19871)	Retrospective cohort	ICD-10: K75.8, K76.0	Adult patients (≥ 18 years) with an initial diagnosis of NAFLD/NASH without liver cirrhosis	58.5 (14.2)	ICD-10: F32, F33	The study showed that, 21.2% of patients with NAFLD and 18.2% of controls were diagnosed with depression (P < 0.001). In regression analysis, the HR for incidence of depression was 1.21 (P < 0.001).	Moderate
Jung 2019 [24]	Korea	112797 (NAFLD = 31635, Non NAFLD = 81162)	Retrospective cohort	The presence and degree of NAFLD were defined according to the abdominal US with a 3.5-MHz transducer	Korean men and women undergoing a medical health check-up program at the Health Promotion center	41.81 (7.4)	The depression status was measured using the Center for Epidemiological Studies-Depression (CES-D) questionnaire	Results showed that in unadjusted model, the presence and severity of NAFLD was not significantly associated with depressive symptoms. However, in the fully adjusted model, ORs for depression increased degree of ultrasonographically detected NAFLD. An association was also observed between depression and FLI ≥ 60: 1.15 [1.02-1.29].	Low
Balp 2019 [25]	Multinational (Germany, France, Spain)	79451 (NAFLD = 184, Non NAFLD = 79267)	Retrospective cohort	Self-reported physician diagnoses	General adult population representative sample of general population with varying health status	54.5 (13.1)	Self-reported physician diagnoses	Patients with NASH reported significantly higher prevalence of depression than the general population (NASH: 31.20% and general population: 19.60%, *p*-value = 0.001).	Moderate
Elwing 2006 [26]	USA	72 (NAFLD = 36, Non NAFLD = 36)	Retrospective, case-control	Histology	All adult patients with histologic evidence of NASH on liver biopsy that could be identified through billing records	51.4 (2)	DSM-IV	Increased lifetime rates of Depressive Disorder in NAFLD subjects compared with an obese comparison and after controlling for confounders was noted to be (OR: 3.8, CI: 1.4-10.2, *p*-value = 0.018).	Low
Lee 2013 [13]	USA	9675 (NAFLD = 497, Non NAFLD = 9178)	Retrospective	NAFLD was defined by the absence of any other causes of CLD as well as by the presence of elevated liver enzymes	18 years or older population	49.6 (0.72)	Patient Health Questionnaire (PHQ-9)	NAFLD was associated with an increased risk of depression.	Moderate
Lee 2021 [27]	Korea	4688 (Depression = 422, Not depressed = 4266)	Cross-sectional study	NAFLD was defined by using a validated hepatic steatosis index that was calculated as 8 × ALT/AST ratio + body mass index	Aged 19 years and older	50.1 (1.1)	PHQ-9 questionnaire Korean version	Depression was a significant predictor of NAFLD (OR = 1.63; 95% CI, 1.26-2.10; P < 0.001).	Low

Kim 2019 [12]	USA	10484 (NAFLD = 3481, Non NAFLD = 7003)	Retrospective	NAFLD was defined using the US Fatty Liver Index (USFLI), Hepatic Steatosis Index (HSI) and Fatty Liver Index (FLI)	Adult patients (age > 20 years) who underwent laboratory examinations at a mobile examination centre	49.5 (0.6)	Patient Health Questionnaire (PHQ-9)	Compared to subjects without depression, those with depression were 1.6-2.2-fold more likely to have NAFLD.	Low
Ng 2022 [28]	USA	21414 (NAFLD = 6726, Non NAFLD = 14688)	Retrospective	Based on American Association for the Study of Liver Disease (AASLD) guidelines for NAFLD	18 years or older population	44.81 (IQR: 28.00 to 60.00)	Patient Health Questionnaire (PHQ-9)	The risk of depression in NAFLD was 12% higher compared to non-NAFLD individuals (RR: 1.12, CI: 1.00-1.26, P = 0.04). NAFLD individuals with depression were more likely to be older, females, Hispanics or Caucasians, diabetic, and have higher BMI.	Low
Kamari 2023 [29]	Iran	7114 (NAFLD = 2456, Non NAFLD = 4658)	Cross-sectional study	NAFLD was defined using the FLI	18 years or older population	45.78 (7.80)	Self-reported drug use	The odds of NAFLD in female participants with depression were 71% higher than in non-depressed participants (OR: 1.71, 95% CI: 1.06-2.64).	Moderate
Tutunchi 2021 [30]	Iran	210 (NAFLD = 95, Non NAFLD = 115)	Case-control study	USG	Included subjects aged from 20 to 50 years old, and those with ultrasound-diagnosed NAFLD for the cases, and those without NAFLD for the controls	47.3 (6.2)	The Beck Depression Inventory (BDI)	NAFLD was associated with an increased risk of depression.	Low
Tomeno 2015 [31]	Japan	258	Prospective cohort	Histology	18 years or older population	50.2 (14.14)	DSM-IV	Depression was noted among 12.4% of cases reported with NAFLD.	Low
Sayiner 2020 [32]	USA	1980950	Retrospective cohort	ICD-10	Individuals 65 or older	70.11 (11.13)	ICD-10	Prevalence of depression in NAFLD patients is 5.84%. Odds ratio for 1-year all-cause mortality in NAFLD patients comorbid with depression is 1.07 (CI: 1.05-1.09).	Moderate
Weinstein 2011 [11]	USA	184	Retrospective cohort	Clinical diagnosis and Histology	18 years or older population	46.7 (11.2)	By asking the patients if they were diagnosed with depression (a yes/no choice) and cross checked with medications	Increased prevalence of depression in patients with NAFLD in comparison with the general population. (NAFLD: 27.1 % vs. general population: 2-5%).	Low
Fernandez 2020 [33]	Cuba	221	Retrospective cohort	Self-reported and histology	18 years or older population	54 (11.3)	Self-reported	High prevalence of depression in patients with NAFLD, but was not statistically significant (*p*-value = 0.08).	Moderate
Youssef 2013 [34]	USA	567	Retrospective cohort	Histological diagnosis of NAFLD	18 years or older population	48 (11)	HADS questionnaire	Patients with more severe depressive symptom were associated with higher likelihood of having more severe hepatocyte ballooning.	Low

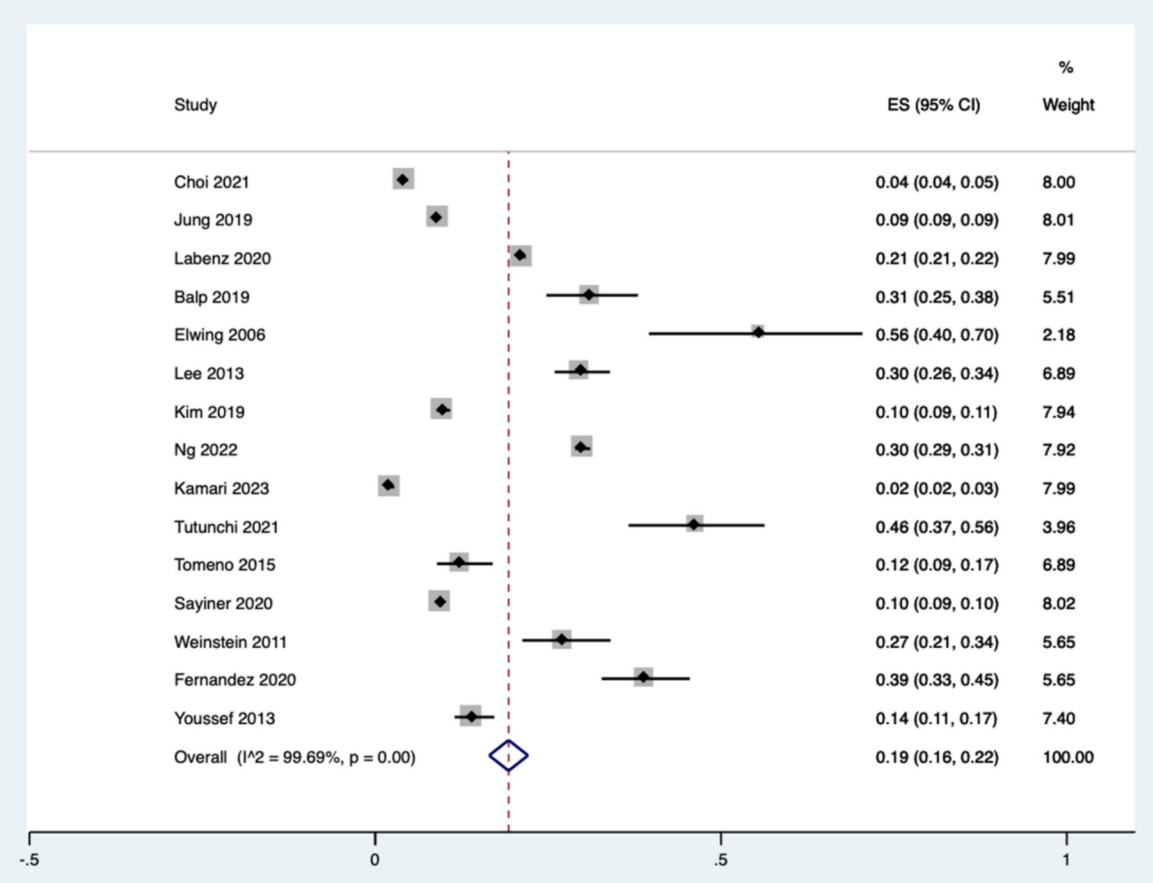

Figure 2. Forest plot showing the prevalence of depression among patients diagnosed with NAFLD.

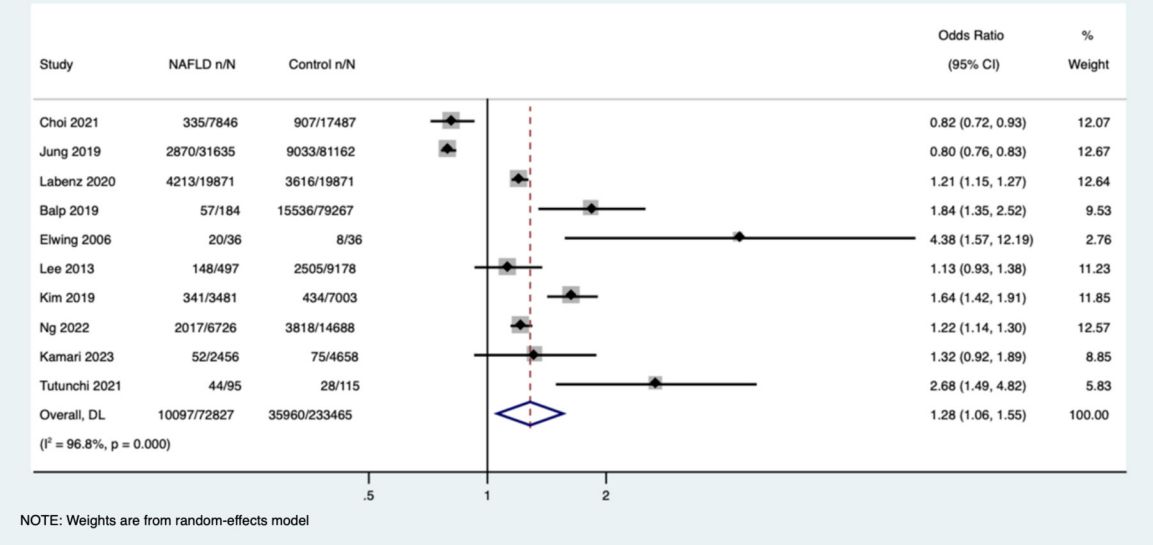

Figure 3. Forest plot showing the risk of depression among patients with NALFD compared to patients without NAFLD.

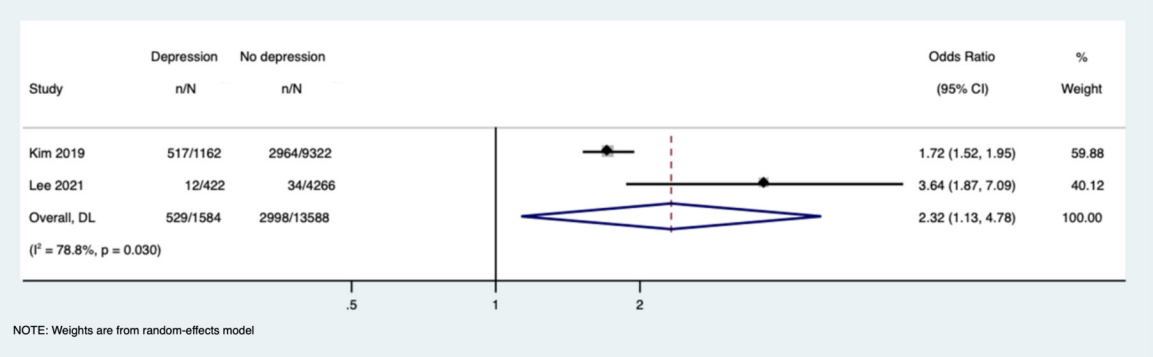

Figure 4. Forest plot showing the risk of NAFLD among patients with depression compared to patients without depression.

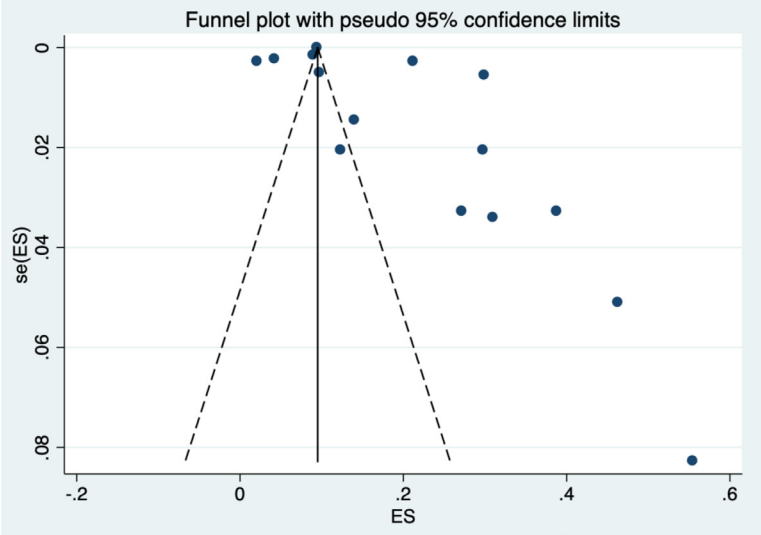

Figure 5. Funnel plot showing publication bias for studies reporting prevalence of depression in patients with NAFLD.

was not performed, as only two studies were included in the analysis.

Publication bias

Publication bias was detected for prevalence estimates (Egger coefficient 17.2, *P*-value < 0.001) but not for the risk of depression in NAFLD patients (Egger coefficient -0.04, *P*-value 0.30). The funnel plots explaining publication bias are shown in **Figures 5** and **6**.

Risk of bias in included studies

Table 1 summarizes the risk of bias, as assessed by the JBI checklist for observational studies. Based on the 9 items of the JBI checklist, the included 16 studies were categorized into low, moderate, and high risk. Of the sixteen included studies, ten had a low risk, and the remaining six had a moderate risk of bias.

Sensitivity analysis

Sensitivity analysis revealed no difference in prevalence estimates or risk estimates between moderate- and low-quality studies. (Supplementary Figures 8 and 9).

Discussion

This meta-analysis included 16 studies that reported on the incidence of depression in NAFLD patients and explored the bidirectional link between NAFLD and depression. The results showed that 19% of patients with NAFLD get diagnosed with depression, and patients with NAFLD have 28% increased chances of getting depression compared to those with no NAFLD. Patients with depression have 2.32 times higher odds of developing NAFLD. The findings of this study highlight a crucial bidirectional association between NAFLD and depression and further emphasize the need for screening for early diagnosis and management.

When compared with previous meta-analyses, this study provides a more comprehensive and updated estimate. Xiao et al. (2021) [15] reported a depression prevalence of 18.2% among NAFLD patients, which was consistent with the estimate of 19% in this study. Similarly, Gu et al. (2022) [16] found a 25% increased

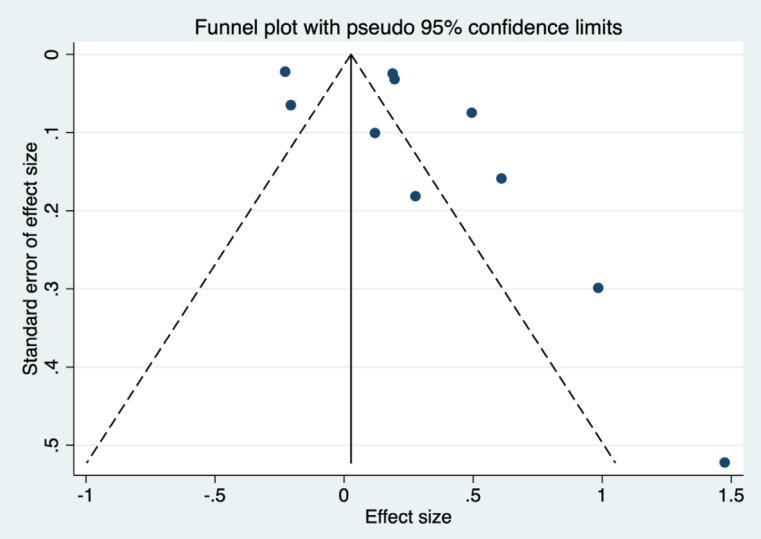

Figure 6. Funnel plot showing publication bias for studies reporting risk of depression among patients with NAFLD.

risk of depression in NAFLD patients, closely aligning with the estimate of 28% reported in this study. However, both meta-analyses included fewer studies (ten and seven, respectively), limiting their statistical power. This study incorporates a larger dataset, enabling more robust estimates and a deeper understanding of the bidirectional nature of this relationship.

While there is still a lack of clarity regarding a possible mechanism behind the bidirectional association between NAFLD and depression, there are several plausible hypotheses. Firstly, systemic inflammation contributes to the pathogenesis of both NAFLD and depression [35]. A state of peripheral insulin resistance and mild systemic inflammation is exacerbated by altered lipid metabolism and oxidative stress, leading to progressive hepatic deposition [22]. Recent studies have shown that depression is also linked to central and peripheral inflammatory mechanisms [36]. Secondly, insulin resistance may play a crucial role in the interplay between depression and NAFLD. Depression may lead to immune-mediated death of the pancreatic beta-cells, leading to insulin resistance and diabetes, which are both significant risk factors for developing NAFLD [37]. Additionally, in NAFLD, chronic inflammation triggers a cascade of events culminating in hepatocellular injury and fibrosis. Inflammatory mediators, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), cross the blood-brain barrier, affecting neuronal function and mood regulation [38]. Another plausible mechanism may involve alterations in gut microbiota composition in NAFLD [39], resulting in dysbiosis and the release of gut-derived metabolites that cross the gut-brain axis, thereby further modulating mood and cognitive function [40]. Depression, in turn, induces alterations in neuroendocrine pathways, leading to hypothalamic-pituitary-adrenal (HPA) axis dysregulation and excessive cortisol release. This cortisol surge may exacerbate insulin resistance and adipose tissue inflammation, thereby creating a conducive environment for the development and progression of NAFLD [41]. Finally, NAFLD and depression share some common mediating mechanisms. Depressive symptoms, characterized by decreased physical activity, poor dietary habits, and disrupted sleep patterns, contribute to the promotion of NAFLD risk factors [42].

The estimates from the current study's results were comparable to those from previously available meta-analyses and other large population-based cohort studies. The reported prevalence of depression among NAFLD patients (19%) is similar to the estimates of Xiao et al. (18.2%) [15]. Additionally, the observed risk of depression among NAFLD patients was 28%, which is in line with estimates from previous studies [15, 16].

This study has several clinical implications. Animal studies have already established a bidirectional association between depression and obesity, which is related to NAFLD [43]. Although many pharmacotherapies for NAFLD have shown promise in phase 3 trials, currently, the mainstays of treatment for NAFLD are weight loss and lifestyle modifications. Therefore, dietary interventions that prevent NAFLD progression may also benefit the mental health of patients with depression [44]. Furthermore, depression in patients with NAFLD is linked to worse outcomes, including a reduced response to medication. It can even be used as a standalone predictor of one-year all-cause mor-

tality. Thus, clinicians should be aware of the higher incidence of depression among NAFLD patients and contemplate lowering the threshold when screening for depression in this patient population.

Strengths and limitations

This review is among the very few studies that have tried to establish the bidirectional association between NAFLD and depression. The review included a comprehensive list of 16 studies with a substantial sample size, reporting the results. The subgroup and sensitivity analyses were used to assess the possibility of publication bias, further adding to the validity of the findings.

Nevertheless, the study has some limitations. High heterogeneity observed between studies may be due to variations in geographic regions, clinical settings, methods used to assess depression (e.g., self-reported questionnaires vs. clinical diagnosis), and definitions used to diagnose both depression and NAFLD. While subgroup analyses were performed to explore potential sources of heterogeneity, future studies should aim for more standardized diagnostic approaches to enhance comparability and consistency. Another limitation is the observational nature of the included studies, which restricts the ability to establish causality. While the findings support a bidirectional relationship, longitudinal cohort studies and interventional trials are needed to confirm the causal mechanisms underlying this association. Additionally, potential confounding factors such as lifestyle behaviors, medication use, and genetic predisposition were not consistently controlled for across studies, which may have influenced the results. Future research should focus on elucidating the precise biologic pathways linking non-alcoholic fatty liver disease (NAFLD) and depression, particularly through mechanistic studies on inflammation, insulin resistance, and alterations in gut microbiota.

Conclusion

This study provided compelling evidence for a bidirectional association between NAFLD and depression. The findings have reported that almost one in every five individuals with NAFLD develops depression.

Disclosure of conflict of interest

None.

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Supplementary Appendix

Search strategy

a. PUBMED

S.NO	SEARCH TERMS	RESULTS
#1	Search: ((Depression) AND (non alcoholic fatty liver disease)) AND (NAFLD) (“depressed”[All Fields] OR “depression”[MeSH Terms] OR “depression”[All Fields] OR “depressions”[All Fields] OR “depressions”[All Fields] OR “depressive disorder”[MeSH Terms] OR (“depressive”[All Fields] AND “disorder”[All Fields]) OR “depressive disorder”[All Fields] OR “depressivity”[All Fields] OR “depressive”[All Fields] OR “depressively”[All Fields] OR “depressiveness”[All Fields] OR “depressives”[All Fields]) AND (“non alcoholic fatty liver disease”[MeSH Terms] OR (“non alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non alcoholic fatty liver disease”[All Fields] OR (“non”[All Fields] AND “alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non alcoholic fatty liver disease”[All Fields]) AND (“naflds”[All Fields] OR “non alcoholic fatty liver disease”[MeSH Terms] OR (“non alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non alcoholic fatty liver disease”[All Fields] OR “nafld”[All Fields]) Translations Depression: “depressed”[All Fields] OR “depression”[MeSH Terms] OR “depression”[All Fields] OR “depressions”[All Fields] OR “depression’s”[All Fields] OR “depressive disorder”[MeSH Terms] OR (“depressive”[All Fields] AND “disorder”[All Fields]) OR “depressive disorder”[All Fields] OR “depressivity”[All Fields] OR “depressive”[All Fields] OR “depressively”[All Fields] OR “depressiveness”[All Fields] OR “depressives”[All Fields] non alcoholic fatty liver disease: “non-alcoholic fatty liver disease”[MeSH Terms] OR (“non-alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non-alcoholic fatty liver disease”[All Fields] OR (“non”[All Fields] AND “alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non alcoholic fatty liver disease”[All Fields] NAFLD: “naflds”[All Fields] OR “non-alcoholic fatty liver disease”[MeSH Terms] OR (“non-alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non-alcoholic fatty liver disease”[All Fields] OR “nafld”[All Fields]	176
#2	Search: (((((Depression) OR (Depressed)) AND (NAFLD)) AND (Hepatic steatosis)) OR (Fatty steatosis)) AND (OBSERVATIONAL STUDIES) ((((“depressed”[All Fields] OR “depression”[MeSH Terms] OR “depression”[All Fields] OR “depressions”[All Fields] OR “depression s”[All Fields] OR “depressive disorder”[MeSH Terms] OR (“depressive”[All Fields] AND “disorder”[All Fields]) OR “depressive disorder”[All Fields] OR “depressivity”[All Fields] OR “depressive”[All Fields] OR “depressively”[All Fields] OR “depressiveness”[All Fields] OR “depressives”[All Fields] OR (“depressed”[All Fields] OR “depression”[MeSH Terms] OR “depression”[All Fields] OR “depressions”[All Fields] OR “depression s”[All Fields] OR “depressive disorder”[MeSH Terms] OR (“depressive”[All Fields] AND “disorder”[All Fields]) OR “depressive disorder”[All Fields] OR “depressivity”[All Fields] OR “depressive”[All Fields] OR “depressively”[All Fields] OR “depressiveness”[All Fields] OR “depressives”[All Fields])) AND (“naflds”[All Fields] OR “non alcoholic fatty liver disease”[MeSH Terms] OR (“non alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non alcoholic fatty liver disease”[All Fields] OR “nafld”[All Fields]) AND (“fatty liver”[MeSH Terms] OR (“fatty”[All Fields] AND “liver”[All Fields]) OR “fatty liver”[All Fields] OR (“hepatic”[All Fields] AND “steatosis”[All Fields]) OR “hepatic steatosis”[All Fields])) OR ((“fatties”[All Fields] OR “fatty”[All Fields]) AND (“fatty liver”[MeSH Terms] OR (“fatty”[All Fields] AND “liver”[All Fields]) OR “fatty liver”[All Fields] OR “steatosis”[All Fields]))) AND (“observational study”[Publication Type] OR “observational studies as topic”[MeSH Terms] OR “observational studies”[All Fields]) Translations Depression: “depressed”[All Fields] OR “depression”[MeSH Terms] OR “depression”[All Fields] OR “depressions”[All Fields] OR “depression’s”[All Fields] OR “depressive disorder”[MeSH Terms] OR (“depressive”[All Fields] AND “disorder”[All Fields]) OR “depressive disorder”[All Fields] OR “depressivity”[All Fields] OR “depressive”[All Fields] OR “depressively”[All Fields] OR “depressiveness”[All Fields] OR “depressives”[All Fields] Depressed: “depressed”[All Fields] OR “depression”[MeSH Terms] OR “depression”[All Fields] OR “depressions”[All Fields] OR “depression’s”[All Fields] OR “depressive disorder”[MeSH Terms] OR (“depressive”[All Fields] AND “disorder”[All Fields]) OR “depressive disorder”[All Fields] OR “depressivity”[All Fields] OR “depressive”[All Fields] OR “depressively”[All Fields] OR “depressiveness”[All Fields] OR “depressives”[All Fields] NAFLD: “naflds”[All Fields] OR “non-alcoholic fatty liver disease”[MeSH Terms] OR (“non-alcoholic”[All Fields] AND “fatty”[All Fields] AND “liver”[All Fields] AND “disease”[All Fields]) OR “non-alcoholic fatty liver disease”[All Fields] OR “nafld”[All Fields] Hepatic steatosis: “fatty liver”[MeSH Terms] OR (“fatty”[All Fields] AND “liver”[All Fields]) OR “fatty liver”[All Fields] OR (“hepatic”[All Fields] AND “steatosis”[All Fields]) OR “hepatic steatosis”[All Fields] Fatty: “fatties”[All Fields] OR “fatty”[All Fields] steatosis: “fatty liver”[MeSH Terms] OR (“fatty”[All Fields] AND “liver”[All Fields]) OR “fatty liver”[All Fields] OR “steatosis”[All Fields] OBSERVATIONAL STUDIES: “observational study”[Publication Type] OR “observational studies as topic”[MeSH Terms] OR “observational studies”[All Fields]	860

#3	Search: ((((Depression) OR (Depressed)) AND (NAFLD)) AND (Hepatic steatosis)) AND (Fatty steatosis) ("depressed"[All Fields] OR "depression"[MeSH Terms] OR "depression"[All Fields] OR "depressions"[All Fields] OR "depression s"[All Fields] OR "depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depressivity"[All Fields] OR "depressive"[All Fields] OR "depressively"[All Fields] OR "depressiveness"[All Fields] OR "depressives"[All Fields] OR ("depressed"[All Fields] OR "depression"[MeSH Terms] OR "depression"[All Fields] OR "depressions"[All Fields] OR "depression s"[All Fields] OR "depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depressivity"[All Fields] OR "depressive"[All Fields] OR "depressively"[All Fields] OR "depressiveness"[All Fields] OR "depressives"[All Fields])) AND ("nafIds"[All Fields] OR "non alcoholic fatty liver disease"[MeSH Terms] OR ("non alcoholic"[All Fields] AND "fatty"[All Fields] AND "liver"[All Fields] AND "disease"[All Fields]) OR "non alcoholic fatty liver disease"[All Fields] OR "nafld"[All Fields]) AND ("fatty liver"[MeSH Terms] OR ("fatty"[All Fields] AND "liver"[All Fields]) OR "fatty liver"[All Fields] OR ("hepatic"[All Fields] AND "steatosis"[All Fields]) OR "hepatic steatosis"[All Fields]) AND (("fatties"[All Fields] OR "fatty"[All Fields]) AND ("fatty liver"[MeSH Terms] OR ("fatty"[All Fields] AND "liver"[All Fields]) OR "fatty liver"[All Fields] OR "steatosis"[All Fields])) Translations Depression: "depressed"[All Fields] OR "depression"[MeSH Terms] OR "depression"[All Fields] OR "depressions"[All Fields] OR "depression's"[All Fields] OR "depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depressivity"[All Fields] OR "depressive"[All Fields] OR "depressively"[All Fields] OR "depressiveness"[All Fields] OR "depressives"[All Fields] Depressed: "depressed"[All Fields] OR "depression"[MeSH Terms] OR "depression"[All Fields] OR "depressions"[All Fields] OR "depression's"[All Fields] OR "depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depressivity"[All Fields] OR "depressive"[All Fields] OR "depressively"[All Fields] OR "depressiveness"[All Fields] OR "depressives"[All Fields] NAFLD: "nafIds"[All Fields] OR "non-alcoholic fatty liver disease"[MeSH Terms] OR ("non-alcoholic"[All Fields] AND "fatty"[All Fields] AND "liver"[All Fields] AND "disease"[All Fields]) OR "non-alcoholic fatty liver disease"[All Fields] OR "nafld"[All Fields] Hepatic steatosis: "fatty liver"[MeSH Terms] OR ("fatty"[All Fields] AND "liver"[All Fields]) OR "fatty liver"[All Fields] OR ("hepatic"[All Fields] AND "steatosis"[All Fields]) OR "hepatic steatosis"[All Fields] Fatty: "fatties"[All Fields] OR "fatty"[All Fields] steatosis: "fatty liver"[MeSH Terms] OR ("fatty"[All Fields] AND "liver"[All Fields]) OR "fatty liver"[All Fields] OR "steatosis"[All Fields]	194
#3	#1 OR #2 OR #3	860

b. SCIENCE DIRECT: 1229

((Depression) AND (non-alcoholic fatty liver disease)) AND (NAFLD)

c. GOOGLE SCHOLAR: 1567

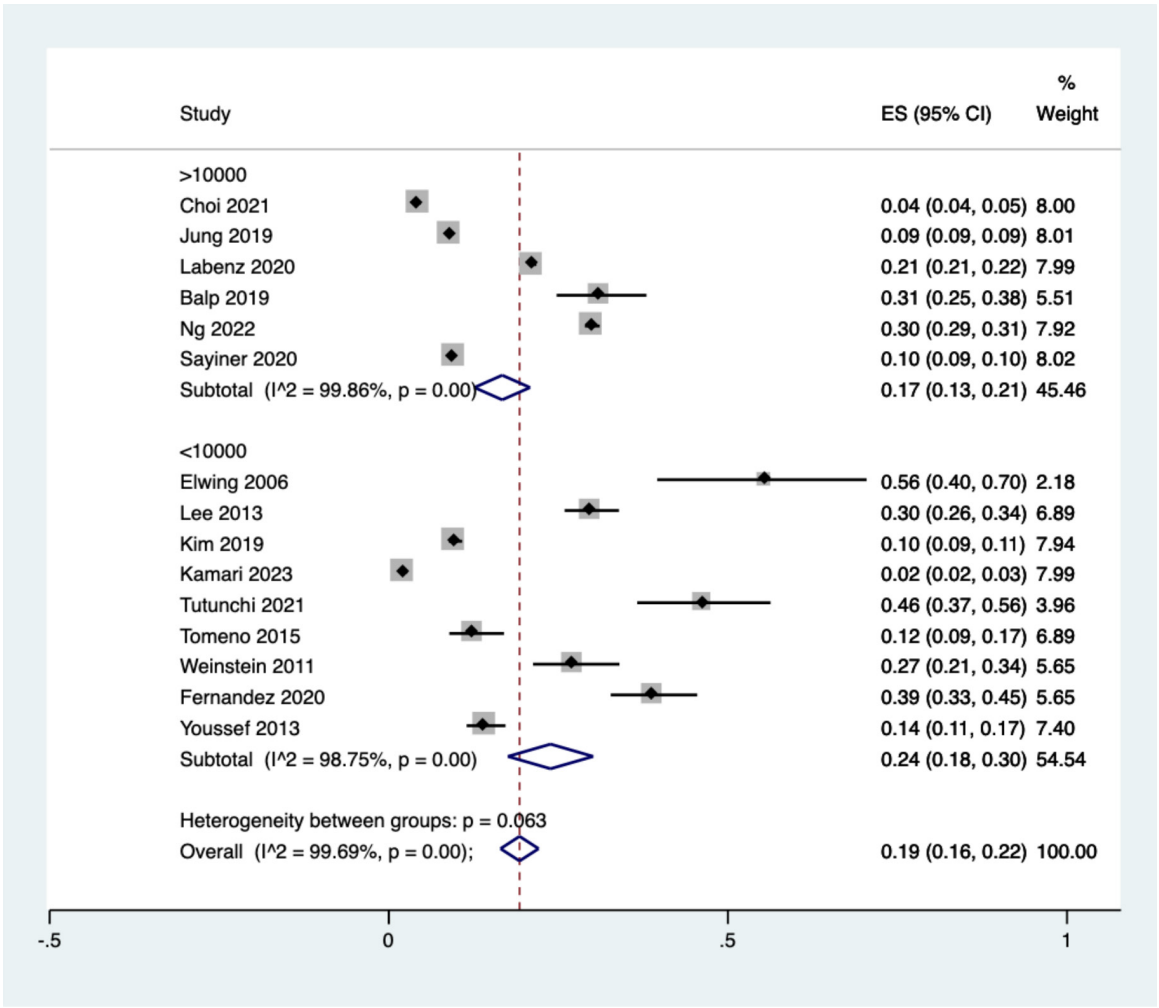
Depression
Depressed
Non-alcoholic fatty liver disease
NAFLD
Hepatic steatosis
Fatty steatosis
Cohort studies
Case-control studies
Cross-sectional studies
Observational studies

Supplementary Table 1. PRISMA_2020_checklist

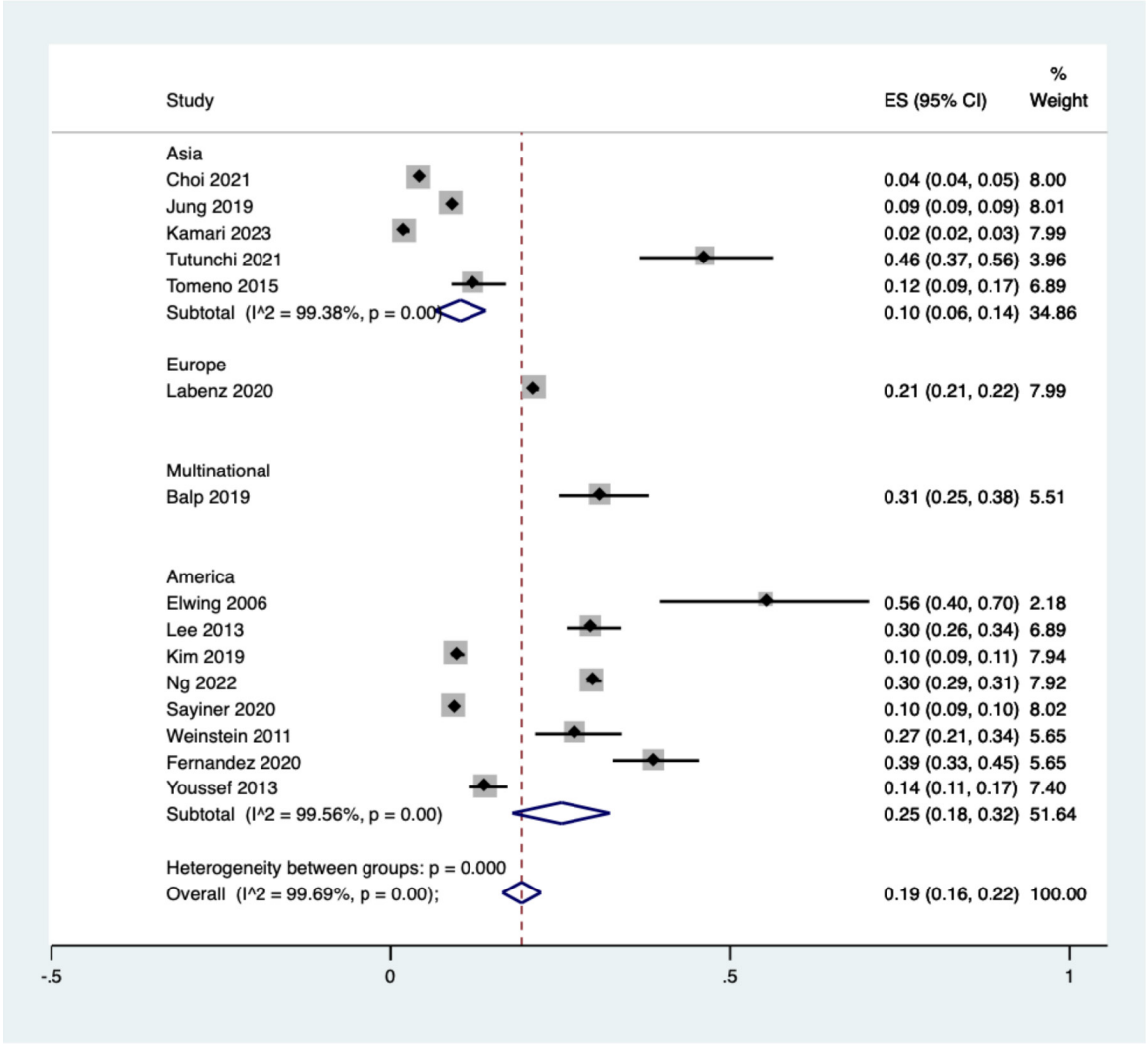
Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P3, 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P3, 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P3, 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P4, 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	P4, 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P4, 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P4, 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P4, 5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P4, 5, Supplementary
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Nil

RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	P5, 6, 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	P5, 6, 7
Study characteristics	17	Cite each included study and present its characteristics.	P5, 6, 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	P6, 7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P5, 6, 7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P5, 6, 7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P5, 6, 7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P6, 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Nil
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P7, 8
	23b	Discuss any limitations of the evidence included in the review.	P7, 8
	23c	Discuss any limitations of the review processes used.	P8
	23d	Discuss implications of the results for practice, policy, and future research.	P8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	PROSPERO CRD42023457671
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	PROSPERO CRD42023457671
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Nil
Competing interests	26	Declare any competing interests of review authors.	Nil declared
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Nil

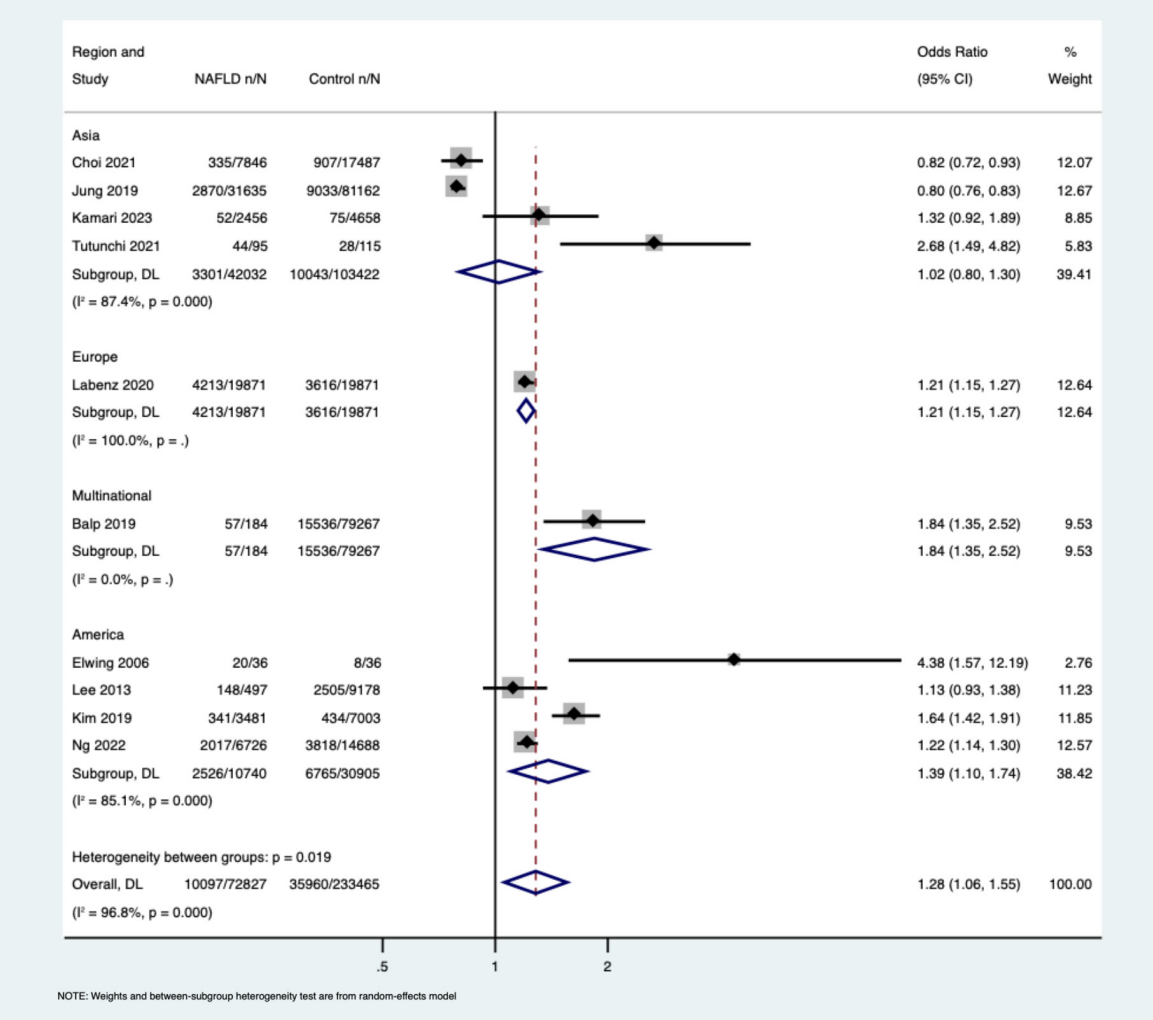
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.



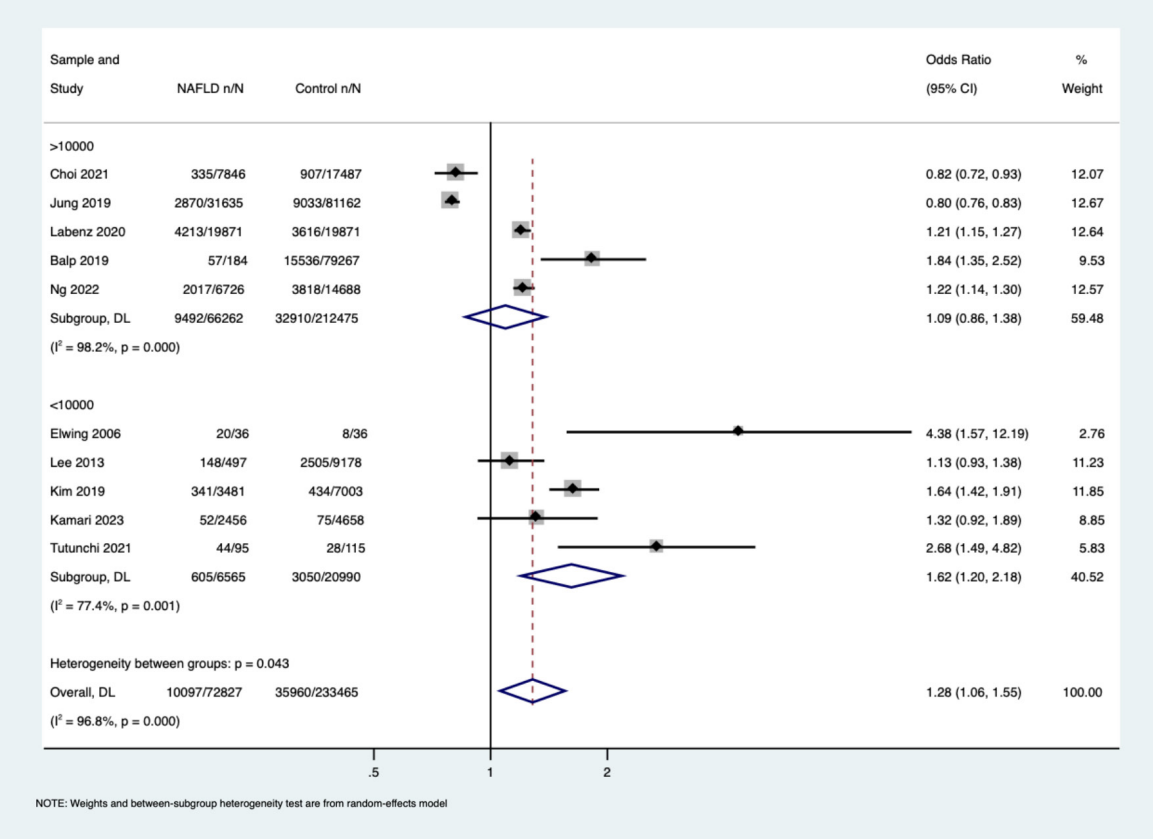
Supplementary Figure 1. Forest plot showing the prevalence of depression among patients diagnosed with NAFLD grouped by sample size.



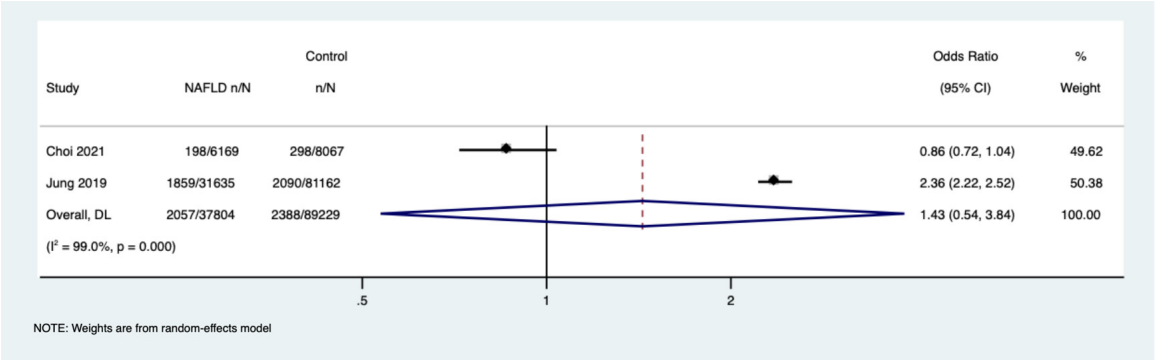
Supplementary Figure 2. Forest plot showing the prevalence of depression among patients diagnosed with NAFLD grouped by region.



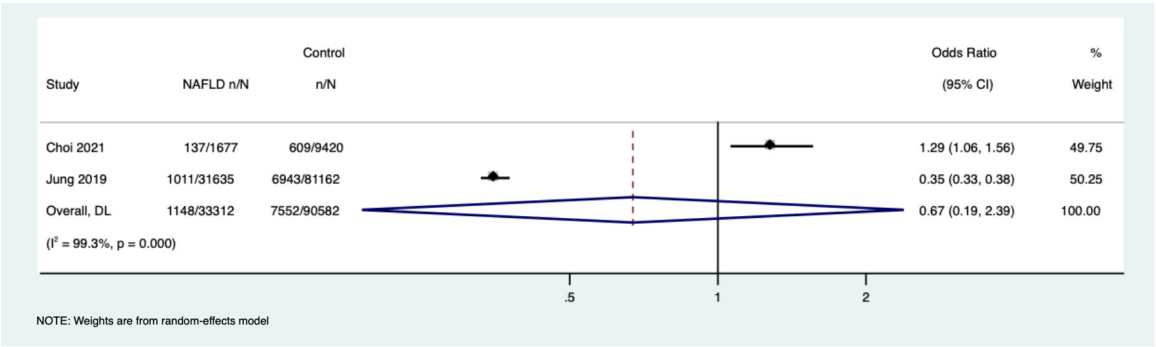
Supplementary Figure 3. Forest plot showing the risk of depression among patients with NALFD patients grouped by region.



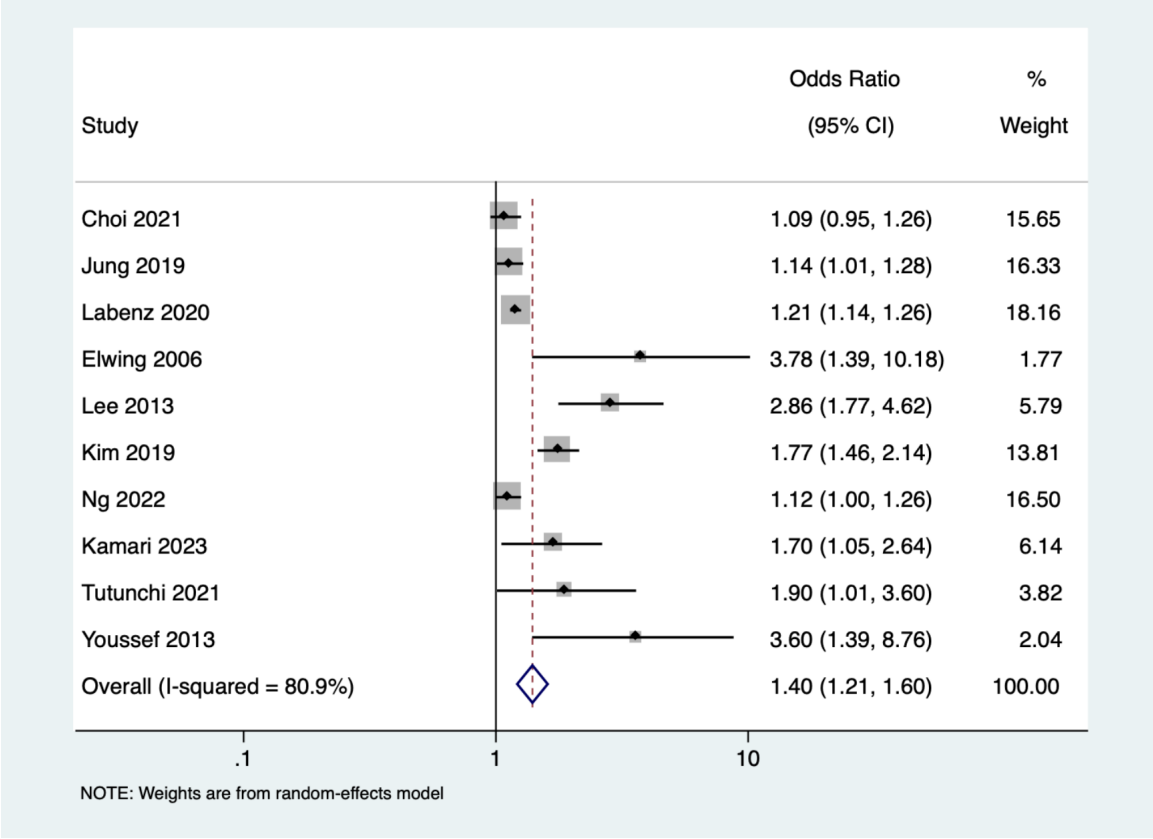
Supplementary Figure 4. Forest plot showing the risk of depression among patients with NALFD patients grouped by sample.



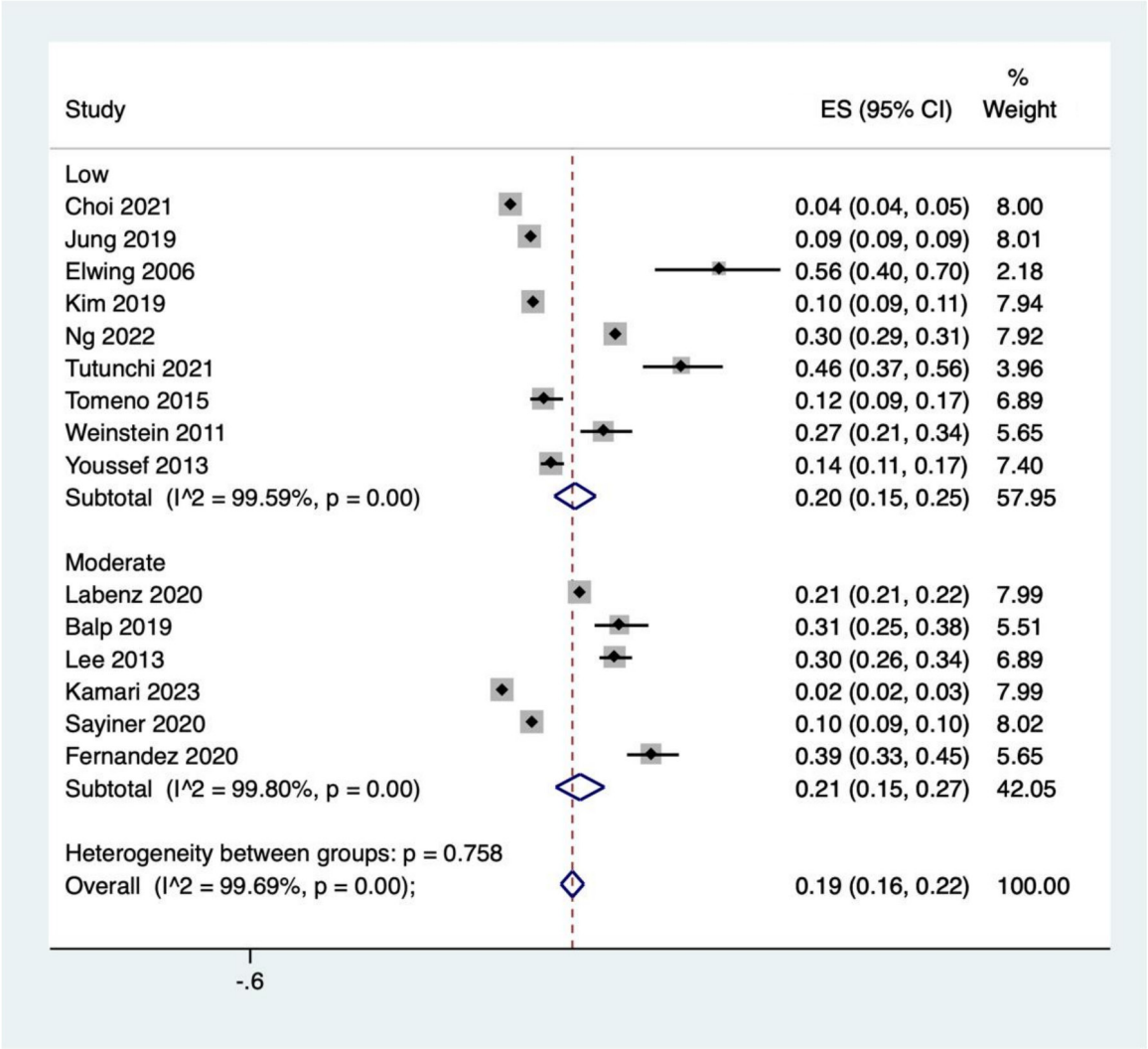
Supplementary Figure 5. Forest plot showing the risk of depression among male NALFD patients.



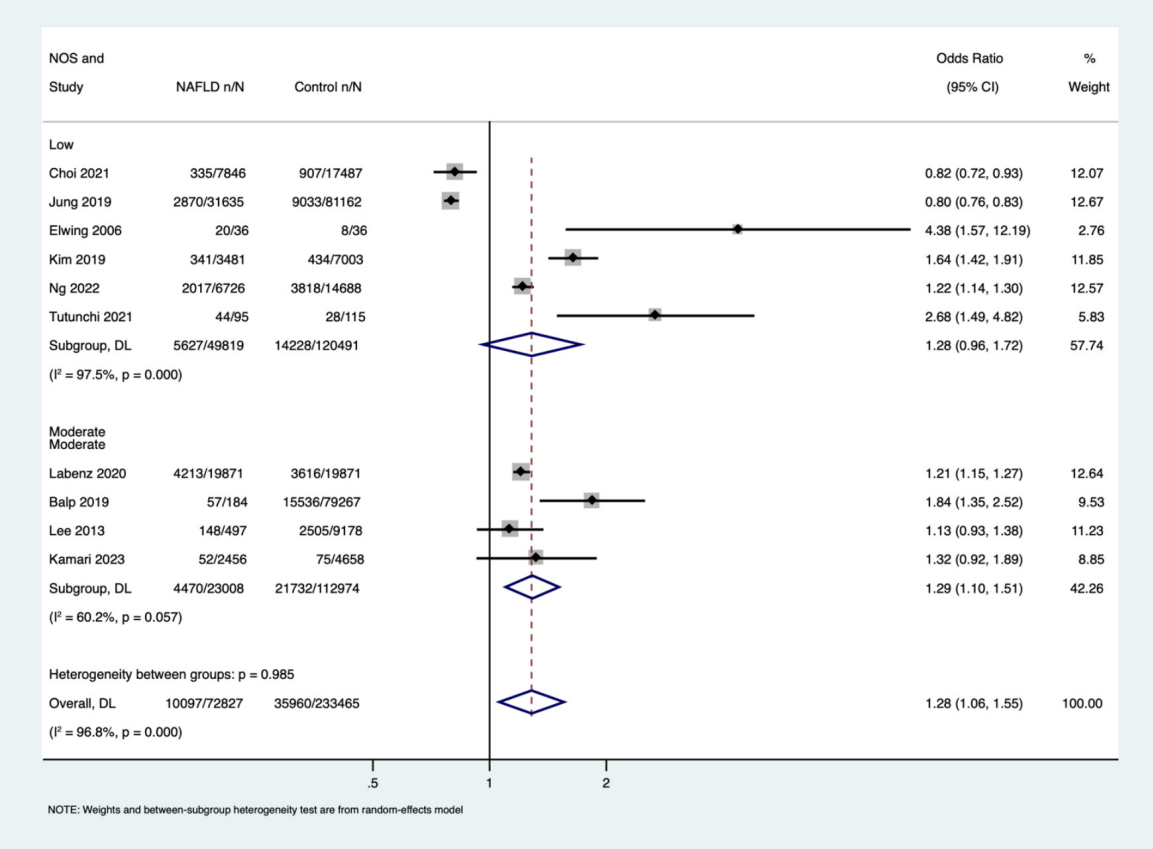
Supplementary Figure 6. Forest plot showing the risk of depression among female NALFD patients.



Supplementary Figure 7. Forest plot showing the prevalence of depression among patients diagnosed with NAFLD sorted by quality of studies.



Supplementary Figure 8. Forest plot showing the prevalence of depression among patients diagnosed with NAFLD sorted by quality of studies.



Supplementary Figure 9. Forest plot showing the risk of depression among patients with NALFD sorted by quality of studies.