The relationship between non-alcoholic fatty liver disease and incidence of chronic kidney disease for diabetic and non-diabetic subjects: A meta-analysis

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Abstract

Introduction. The prevalence of chronic kidney disease (CKD) rises with age and co-morbid diseases such as liver diseases.

Objectives. The main aim of the current meta-analysis is to assess the relationship between Non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease incidence in both diabetic and non-diabetic subjects compared with control.

Materials and methods. A systematic literature search of papers published from January 1, 2005, till April 30, 2022, found 19 studies including 1,111,046 subjects; 310,804 were diagnosed with NAFLD, and 800,242 were non-NAFLD. The measured outcome was the incidence of CKD among NAFLD subjects compared to non-NAFLD subjects in diabetic and non-diabetic subjects. Dichotomous analysis methods were used within the random effects model to calculate the odds ratio (OR) with 95% confidence intervals (95% CIs).

Results. The incidence of CKD is highly significant in NAFLD subjects compared with controls (OR: 1.95; 95% CI: 1.65–2.31). The diabetic non-NAFLD subjects showed a significantly increased incidence of CKD compared to the non-diabetic subjects with NAFLD (OR: 1.79; 95% CI: 1.35–2.38).. In addition, the incidence of CKD was significantly higher in the NAFLD group compared with the non-NAFLD non-diabetic subjects (OR: 2.52; 95% CI: 1.91–3.32). Diabetes acts as an independent risk factor for CKD, as proven by a significant increase in incidence of diabetic subjects compared to non-diabetic NAFLD subjects (OR: 1.82; 95% CI: 1.15–2.88).

Conclusions. Non-alcoholic fatty liver disease is significantly related to an increased incidence of CKD, which is significantly higher in diabetic subjects.

Key words: diabetes, NAFLD, kidney function, chronic kidney disease

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Introduction

The prevalence of chronic kidney disease (CKD) rises with age, affecting around 25% of those aged over 65 in the Western world.[1] Consistent with the epidemic expansion of major risk factors including aging, diabetes, obesity, metabolic syndrome, smoking, and hypertension, the prevalence of CKD is increasing.[2,3] More than 400,000 Americans are already undergoing renal replacement therapy, and this figure is expected to increase to 2,200,000 by 2030.[2] The majority of patients with CKD die from cardiovascular disease (CVD) before the renal replacement treatment can begin,[4] making CKD a key risk factor for end-stage renal disease (ESRD), as well as CVD. The health effects of CKD may be minimized by an early detection and treatment that slows the progression of renal disease and reduces CVD.[3] Early referral efforts for patients with stage 3 of CKD are the most useful. Despite these facts, CKD is frequently misdiagnosed; according to the Third National Health and Nutrition Examination Survey (NHANES III), only 8.2% of persons with stage 3 of CKD were aware of their disease.[5] Due to the disease's high morbidity and mortality rates, as well as high related healthcare expenditures, researchers are searching for novel modifiable risk factors for CKD. Thirty percent of the adult population has non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome.[6] Sixty to seventy percent of those with diabetes and obesity are affected. Under normal conditions, reactive oxygen species (ROS) are a key part of cell signaling, which is involved in cell growth, division, death, and immune defense in many cell lineages, including renal cells. However, in diabetes, the kidneys produce too much ROS. This causes inflammation which changes the structure and function of the kidneys and eventually leads to ESRD. The production of ROS caused by hyperglycemia encourages the recruitment of many inflammatory cells and increases the production of inflammatory cytokines, growth factors and transcription factors that are involved in the pathological processes of diabetic nephropathy.[7] Non-alcoholic fatty liver disease can range histologically from simple steatosis to non-alcoholic steatohepatitis (NASH), the latter of which can involve significant fibrosis. Independently of metabolic syndrome and existing risk factors, NAFLD raises the risk of cirrhosis, which is primarily limited to NASH, as well as CVD.[8] Experiments and epidemiological research are accumulating evidence indicating that NAFLD and CKD interact and share pathogenic mechanisms.[9] In the published literature, small study populations and marginal relationships between NAFLD and recognized risk factors for CKD cast doubt on the existence of a link between NAFLD and CKD.

Objectives

The main aim of the current meta-analysis is to assess the relationship between NAFLD and CKD incidence in diabetic and non-diabetic subjects compared with controls.

Materials and methods

Based on the epidemiological declaration, a methodology was developed and the eligible studies were analyzed.

Criteria for study selection and eligibility criteria of the study

The purpose of the current meta-analysis was to examine the association between NAFLD and the occurrence of CKD in diabetic and non-diabetic subjects compared with controls (non-NAFLD subjects) using statistical methods, such as frequency rate, odds ratio (OR), relative risk, or mean difference (MD) with a 95% confidence interval (95% CI).

The current meta-analysis was open to studies of any size, but research letters and review articles were not included since they did not provide sufficient evidence of causality to meet the inclusion criteria. The conceptualization of the meta-analysis is presented in Fig. 1. Diabetic and non-diabetic patients with and without NAFLD were compared for their sensitivity to CKD.

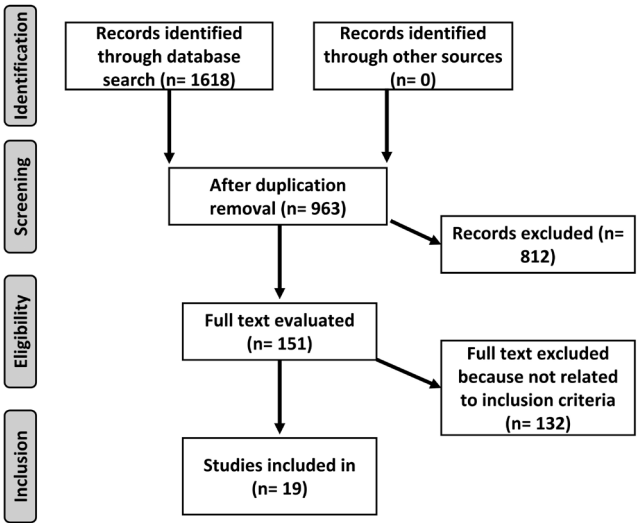

Fig. 1. Illustration diagram presenting the mode of meta-analysis

Inclusion criteria

Randomized controlled trials, prospective studies and retrospective studies were included in this study. Studies comparing NAFLD and controls conducted on human population and estimating the role of NAFLD and diabetes in the development of CKD (glomerular filtration rate

(GFR) < 60 mL/min/1.73 m^2) were taken into account. Finally, studies that examine the prevalence of CKD in people with NAFLD who are either diabetic or non-diabetic were also included.

Exclusion criteria

Studies excluded from the current analysis were those that did not investigate the impact of NAFLD or diabetes on CKD incidence or did not analyze feeding habits. In addition, studies using outcome measures that are unreliable, incomplete or deceptive were also excluded. Finally, studies that did not compare subjects with NAFLD to subjects without NAFLD, or those that did not compare subjects with diabetes to people without diabetes, were considered low quality and unsuitable for inclusion.

Search strategy, study selection and data extraction

Identification

The search strategy is shown in Table 1. "NAFLD", "CKD", "diabetic", "kidney function", and similar terms were used to conduct a comprehensive literature search in MEDLINE/PubMed, the Cochrane Library, OVID, Embase, and Google Scholar published from January 1, 2005, till April 30, 2022. The PICOS process had been used during the identification and screening of the articles: 1) population (P): NAFLD; 2) intervention/exposure (I): monitoring CKD incidence in NAFLD subjects compared with control for both diabetic and non-diabetic subjects (comparison (C)); 3) outcome (O): incidence of CKD. Study types (S) include both randomized clinical trials and retrospective studies. The EndNote software (Clarivate, London, UK) was used to classify the research publications to eliminate duplicates. To further assess the relationship between NAFLD and CKD incidence in both diabetic and non-diabetic subjects compared with controls, we reviewed all titles and abstract data. All relevant data for this topic were collected from the studies we considered.

Table 1. Strategy of searching scientific databases

Database	Search strategy
PubMed	#1 "non-alcoholic fatty liver disease" (MeSH terms) OR "chronic kidney disease" (MeSH terms) OR "diabetes" (all fields) #2 "kidney function" (MeSH terms) OR "non-diabetic" (all fields) #3 #1 AND #2
Embase	#1 "non-alcoholic fatty liver disease"/exp OR "NAFLD"/exp OR "liver failure"/exp #2 "chronic kidney disease"/exp OR "CKD"/exp #3 #1 AND #2
Cochrane Library	#1 "non-alcoholic fatty liver disease": ti, ab, kw OR "NAFLD": ti, ab, kw OR "liver failure": ti, ab, kw (word variations have been searched) #2 "chronic kidney disease": ti, ab, kw OR "CKD": ti, ab, kw (word variations have been searched) #3 #1 AND #2

ti, ab, kw – terms in the title, abstract or keyword fields; exp – exploded indexing term.

Screening

All of the information relevant to the subjects and the research was recorded into a standardized database. It included the information about the study's setting, primary outcome evaluation, treatment mode, duration, categories, statistical analysis, information source, and qualitative and quantitative evaluation, as well as the first author's surname and the total number of subjects.

The "Risk of Bias Tool" from the Cochrane Reviewer Manger v. 5 (https://training.cochrane.org/online-learning/core-software/revman/revman-5-download) was used to assess the methodology's robustness. The screening process was carried out by 2 authors (YC and WB).

Data extraction

Outcomes to be evaluated from the included studies were the incidences of CKD in NAFLD subjects compared with controls. Data collected from each study had been collected in separate forms by 2 authors working separately (QS and FL); then, the extracted data were compared and evaluated by a 3rd author (KW). Extracted items from each study were authors, year of publication, country of the study, total number of included subjects, number of interventional groups, numbers of the control group, the final conclusion, and outcomes related to the meta-analysis criteria. Next, studies were categorized into subgroup sections according to the measured outcomes from each study.

Data synthesis and analysis

Odds ratios and 95% CIs were determined dichotomously in the statistical analysis utilizing the random effects model. To begin with, the I^2 index was measured from 0% to 100%, whereas the heterogeneity scale included 0%, 25%, 50%, and 75%, representing no, low, moderate, and high levels of heterogeneity, respectively. If the value of I^2 was greater than 50%, the random effect was prioritized over the fixed influence. The fixed model is suitable for use with studies with a high degree of similarities and with low heterogeneity. In the current study, all analyses were carried out using the random model. Forest plots were generated and they showed p-values and I^2 of different subgroup analyses. Since a value of $p < 0.05$ was required to draw any conclusions, we used a subgroup analysis on the first dataset. The publication bias was assessed with the Begg's test and visual examination of funnel plots. The Reviewer

Manager, v. 5.4.1 (The Cochrane Collaboration, Copenhagen, Denmark), was used for the statistical analysis with two-tailed p-values.

Bias risk in the criteria for assessment

The examination of the criteria reveals 3 distinct types of prejudice. In other words, the risk of bias were rated from low (when all quality parameters were met) to moderate (when some of the quality parameters were met but not all) to high (when none of the quality criteria was met or included). The examination of the paper revealed similar anomalies.

Two authors (DM and FL) reviewed the publications independently to evaluate the risk of bias, and a 3rd author (NW) assessed the criteria in case the initial check results were not identical from the 2 authors.

Results

Among the 1618 unique reports, the current meta-analysis included 19 studies[10–28] published between 2008 and 2021 that matched the inclusion criteria. The study groups in these papers consisted of 1,111,046 subjects in total; 310,804 were diagnosed with NAFLD, and 800,242 were non-NAFLD (Table 2).

NAFLD compared to non-NAFLD

The relationship between NAFLD and CKD incidence in diabetic and non-diabetic subjects compared with the control group was assessed, including a total of 18 clinical trials which compared the incidence of CKD in NAFLD subjects to the control group (non-NAFLD). As shown in Fig. 2–5, the incidence of CKD is highly significant ($p < 0.001$) in NAFLD subjects compared to controls (OR: 1.95; 95% CI: 1.65–2.31).

Diabetic subjects

Five studies compared the incidence of CKD between NAFLD and non-NAFLD for diabetic subjects, while 6 studies assessed the impact of diabetes on the incidence of CKD in NAFLD subjects compared with non-diabetic NAFLD subjects as control. The impact of diabetes as comorbidity significantly increased the incidence of CKD in non-diabetic subjects with NAFLD ($p < 0.001$; OR: 1.79; 95% CI: 1.35–2.38) compared with non-NAFLD. Diabetes acts as an independent risk factor for CKD, as proven by a significant increase in CKD incidence for diabetic compared with non-diabetic NAFLD subjects ($p = 0.01$; OR: 1.82; 95% CI: 1.15–2.88).

Non-diabetic subjects

Only 3 studies compared the non-diabetic NAFLD group with the non-NAFLD group of non-diabetic

Table 2. Characteristics of the studies included in the meta-analysis

Study	Year	Country	Total	NAFLD	Non-NAFLD
Adams et al. [11]	2005	USA	402	201	201
Targher et al. [25]	2008	Italy	2103	1421	682
Campos et al. [15]	2008	USA	197	123	74
Chang et al. [17]	2008	South Korea	8329	2516	5813
Hwang et al. [19]	2010	South Korea	1361	748	613
Targher et al. [24]	2010	Italy	160	80	80
Athyros et al. [14]	2010	Greece	720	210	510
Park et al. [21]	2011	USA	562	66	496
Sirota et al. [23]	2012	Italy	11,469	4179	7290
Targher et al. [26]	2012	Italy	343	182	161
Xia et al. [27]	2012	China	1141	477	664
Musso et al. [20]	2012	Italy	80	40	40
Ahn et al. [12]	2013	South Korea	1706	545	1161
El Azeem et al. [10]	2013	Egypt	738	268	470
Park et al. [22]	2019	USA	1,032,497	262,619	769,878
Zhang et al. [28]	2020	China & USA	11,844	4273	7571
Akahane et al. [13]	2020	Japan	3725	1154	2571
Chen et al. [18]	2020	China	29,797	29,797	–
Cao et al. [16]	2021	China	3872	1905	1967
Total			1,111,046	310,804	800,242

NAFLD – non-alcoholic fatty liver disease.

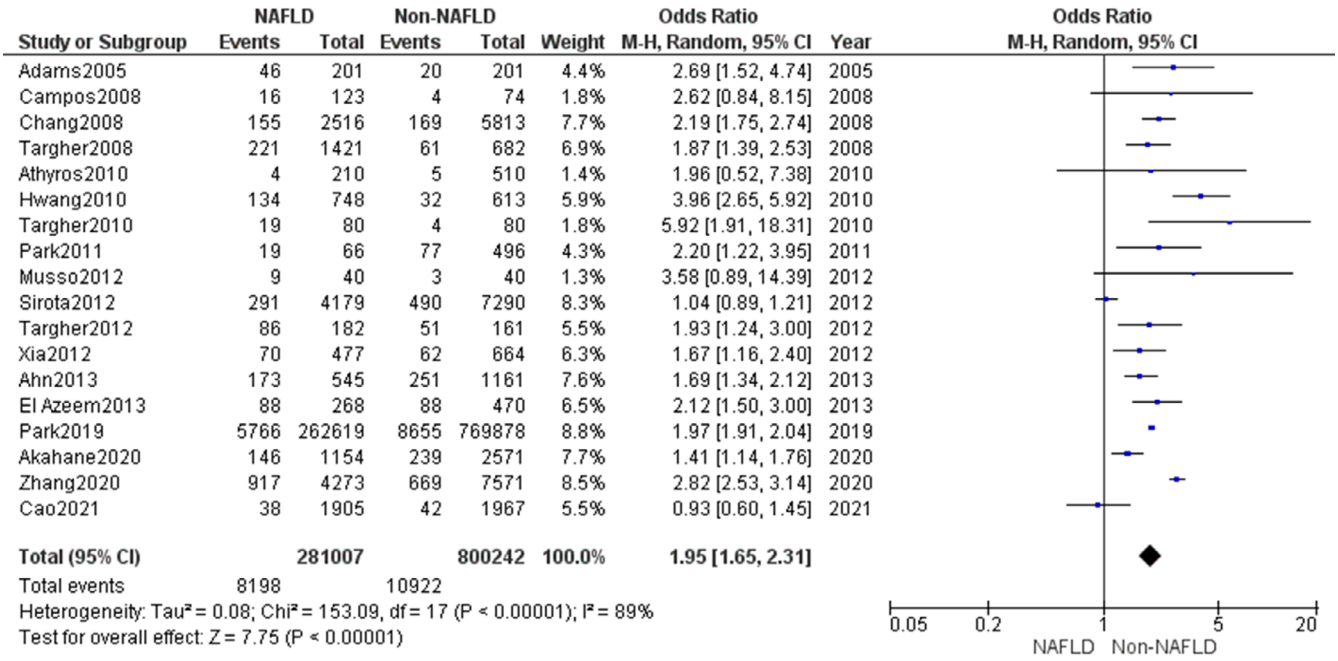

Fig. 2. A forest plot illustrating the impact of non-alcoholic fatty liver disease (NAFLD) compared to non-NAFLD groups on the incidence of chronic kidney disease (CKD)

95% CI – 95% confidence interval; df – degrees of freedom.

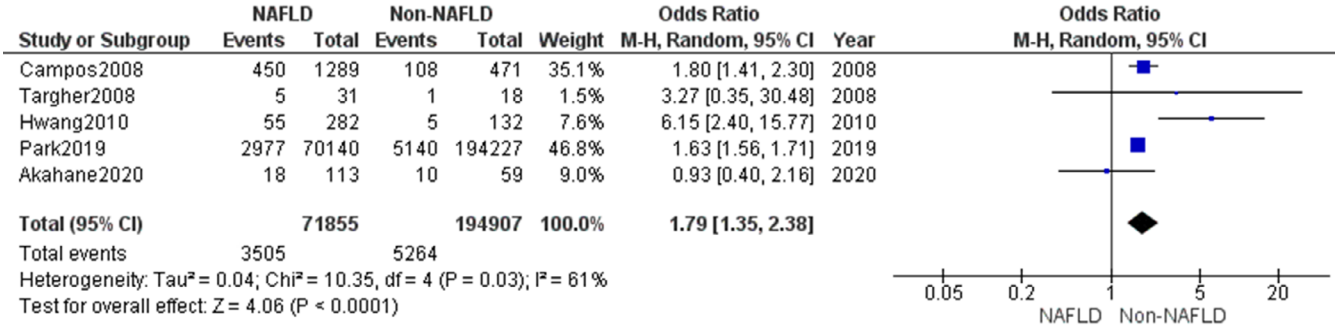

Fig. 3. A forest plot illustrating the impact of diabetic non-alcoholic fatty liver disease (NAFLD) compared to non-NAFLD groups on the incidence of chronic kidney disease (CKD)

95% CI – 95% confidence interval; df – degrees of freedom.

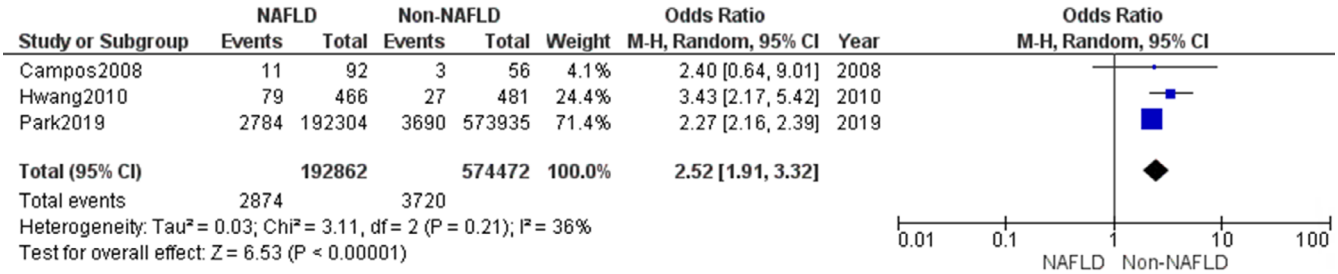

Fig. 4. A forest plot illustrating the impact of non-alcoholic fatty liver disease (NAFLD) compared to non-NAFLD groups on the incidence of chronic kidney disease (CKD)

95% CI – 95% confidence interval; df – degrees of freedom.

subjects. In addition, the incidence of CKD was significantly higher in the NAFLD group compared with non-NAFLD non-diabetic subjects ($p < 0.001$; OR: 2.52; 95% CI: 1.91–3.32).

The Begg's test p-values were statistically non-significant for included studies,[10–28] but these values were variable. The p-value related to the studies comparing NAFLD with non-NAFLD subjects was $p = 0.37$. In addition, for the analysis

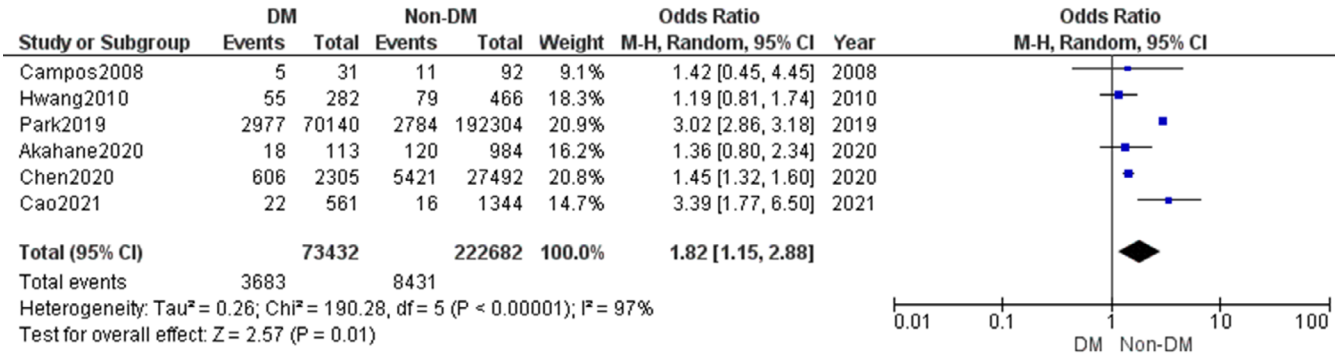

Fig. 5. A forest plot illustrating the impact of non-alcoholic fatty liver disease (NAFLD) subjects with and without diabetes on the incidence of chronic kidney disease (CKD)

95% CI – 95% confidence interval; df – degrees of freedom.

comparing diabetic subjects with control the p-value was 0.82, while for the analysis comparing non-diabetic subjects with control it equalled 0.9. The Begg's test for analysis comparing diabetic with non-diabetic subjects showed p = 0.72. On the other hand, a visual examination of funnel plots showed the presence of publication bias as supported with asymmetric distributions of studies (Fig. 6).

We found that no single study had sufficient data in all 7 categories. Throughout the quality spectrum, the procedures of the included studies varied greatly. The quality of the studies used in this meta-analysis ranged widely. The randomized trial was determined to have insufficient methodological tools.

Discussion

The aim of the study was to measure and assess the relationship between NAFLD and CKD incidence in both diabetic and non-diabetic subjects compared with controls.

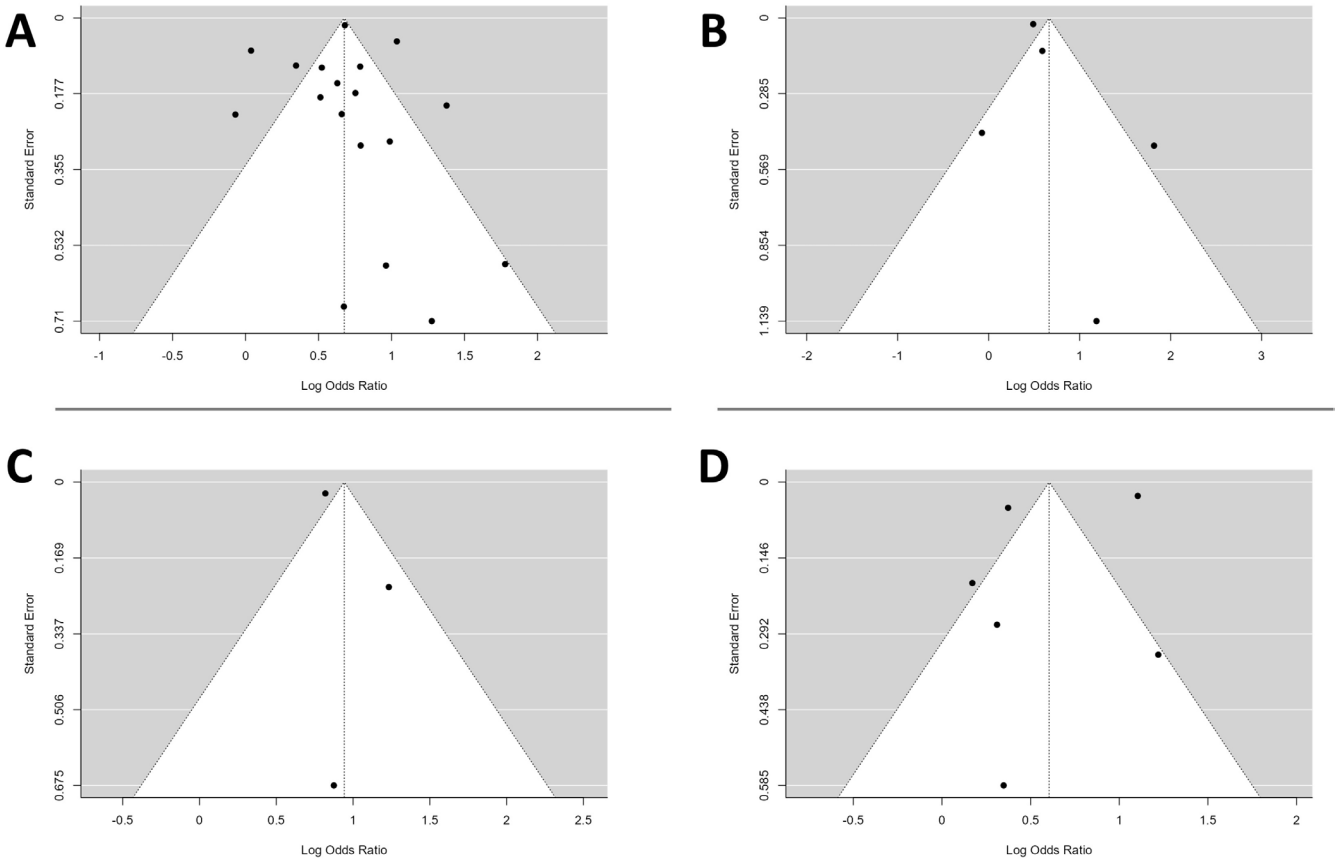

Fig. 6. Funnel plot showing the publication bias for non-alcoholic fatty liver disease (NAFLD) compared to non-NAFLD groups (A), diabetic group compared to control group (B), non-diabetic group compared to control group (C), and diabetic group compared to non-diabetic group (D)

Findings showed that the incidence of CKD is significantly higher in NAFLD subjects compared with controls. The diabetic non-NAFLD subjects showed significantly increased incidence of CKD compared to the non-diabetic subjects with NAFLD (OR: 1.79; 95% CI: 1.35–2.38). In addition, the incidence of CKD was significantly higher in the NAFLD group compared to the non-NAFLD non-diabetic subjects. Diabetes acts as an independent risk factor for CKD, as proven by a significant increase in incidence in diabetic compared with non-diabetic NAFLD subjects. However, because some of the included studies had a small sample size (3 studies had a sample size of less than 200 subjects), a careful analysis of the results is required, implying the necessity for further trials to confirm the current findings; such research could possibly have a substantial effect on the assessment of the intervention impact. The heterogeneity was high for the compared studies, hence subgroup analyses were performed to provide strong evidence for the final conclusion.

Hwang et al. findings imply that NAFLD is associated with an increased frequency of microalbuminuria in persons with prediabetes and newly diagnosed diabetes.[19] This correlation appears to hold even after controlling for potential confounders, such as age, gender, race/ethnicity, education, smoking status, and the presence of other Adult Treatment Panel III (ATP III)-defined components of the metabolic syndrome. Non-alcoholic fatty liver disease may play a role in mediating the elevated risk of CKD in subjects with microalbuminuria. However, as our investigation was limited to people with diabetes or prediabetes, we did not examine the influence of NAFLD on microalbuminuria in subjects with normal glucose levels.

Ahn et al. showed that NAFLD is substantially linked with CKD in the South Korean population aged 50 years or older.[12] The link between NAFLD and CKD remained statistically significant after analyzing for age, sex, current smoking, abdominal obesity, aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), hypertension, diabetes mellitus, hypertriglyceridemia, and low high-density lipoprotein (HDL).

Over a million of Americans are predicted to have ESRD by 2015,[29] as the incidence of CKD continues to skyrocket. In addition to progressing to ESRD, CKD is also a major risk factor for CVD, and most persons with CKD die from CVD before they acquire ESRD. As a result, a lot of effort is being put into identifying potential causes of CKD that can be addressed by lifestyle changes. Non-alcoholic fatty liver disease is a growing risk factor for end-stage liver disease and CVD: the frequency of NASH as the major rationale for liver transplantation has risen from 1.2% to 9.7% in the last decade, becoming the 3rd most prevalent cause for liver transplantation in the USA.[30]

The key findings of our analysis are the following: NAFLD was associated with an increased prevalence and incidence of CKD. In addition, these associations remained statistically significant in diabetic and non-diabetic individuals, as well as in studies adjusting for traditional risk factors for CKD, and were independent of whole body/abdominal obesity and insulin resistance.

Limitations

Many publications were left out of the current meta-analysis because they did not meet the inclusion criteria, which introduced a substantial amount of bias into the study. There was also a considerable uncertainty regarding how to incorporate factors such as gender and race into the analysis. Analyses based on data from previous studies may be flawed due to information gaps. Twenty papers were included in the meta-analysis, 3 of which were very small (under 200 participants). Lost data and unpublished studies may contribute to the problem of influence bias. Studies differed in the average weight of their subjects.

Conclusions

This meta-analysis showed that the incidence of CKD is highly significant in NAFLD subjects compared with controls. The diabetic non-NAFLD subjects showed a significantly increased incidence of CKD compared to the non-diabetic subjects with NAFLD (OR: 1.79; 95% CI: 1.35–2.38). In addition, the incidence of CKD was significantly higher in the NAFLD group compared with non-NAFLD non-diabetic subjects. Diabetes acts as an independent risk factor for CKD, as proven by a significant increase in incidence for diabetic compared with non-diabetic NAFLD subjects. The results of our meta-analysis study did not show any correlation with demographic variables, such as participants' race or gender. Additional research is needed to validate these findings or significantly increase confidence in the effect evaluation because of the small sample sizes in several of the studies included in the meta-analysis.

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