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Review

Nonalcoholic fatty liver disease and the risk of clinical cardiovascular events: A systematic review and meta-analysis

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ABSTRACT

Objective: Numerous studies have assessed the association between Nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD). However, results have been conflicting due to variability in definitions of NAFLD and ascertainment of CVD, often combining clinical and surrogate endpoints. We therefore systematically reviewed published literature to assess the association between NAFLD and clinical cardiovascular events (CVE) and performed a meta-analysis.
Methods: We searched PubMed, Medline, Cochrane, CINAHL, and Web of Science databases using terms "nonalcoholic fatty liver disease", "nonalcoholic steatohepatitis", "cardiovascular disease", and their combinations to identify prospective studies published from inception through March 2016. Data from selected studies was extracted and meta-analysis was then performed using random effects model.
Results: A total of six studies with 25,837 patients (NAFLD: 5953; controls: 19,884) were included in the final analysis. Patients with NAFLD had a significantly higher risk of clinical CVE compared to controls (RR: 1.77; 95% CI: 1.26–2.48, $p < 0.001$). Exclusion sensitivity analysis did not alter the above results. The association remained consistent for subgroups with clinical coronary artery disease (RR: 2.26; 95% CI: 1.04–4.92, $p < 0.001$) and ischemic stroke (RR: 2.09; 95% CI: 1.46–2.98, $p < 0.001$). The risk of cardiovascular mortality was also increased in the NAFLD group (RR 1.46, 95% CI 1.31–1.64, $p < 0.001$).
Conclusion: NAFLD patients have a significantly higher risk for clinical CVE compared to those without. These results need to be confirmed in large prospective studies.

Contents

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease (CLD) in the United States accounting for >75% of patients with CLD based on data from 2008 [1]. Unlike other chronic liver disorders like hepatitis B, hepatitis C and alcoholic liver disease, the prevalence of NAFLD continues to increase, concurrent with national obesity trends [1]. Currently, the estimated prevalence of NAFLD in the United States varies between 10 and 35% based on the diagnostic methods used [2]. NAFLD and cardiovascular disease (CVD) have multiple common risk factors like obesity, diabetes, dyslipidemia, and physical inactivity indicating shared pathogenesis [3]. Furthermore, novel markers of increased atherosclerotic risk like increased inflammation, endothelial dysfunction, and surrogate markers of accelerated atherosclerosis like increased carotid intimal medial thickness have previously been demonstrated in patients with NAFLD [4]. CVD accounts for >30% of deaths in the United States and is the leading cause of mortality in patients with NAFLD, highlighting the importance of recognizing and addressing CVD in patients with NAFLD [5]. To date, studies assessing the risk of cardiovascular disease in NAFLD have yielded disparate results in directionality and strength of the association. Furthermore, most of these studies have frequently combined clinical and subclinical disease limiting the clinical applicability of the results [6,7]. We therefore systematically reviewed published literature assessing the risk of clinical cardiovascular events in patients with NAFLD and performed a meta-analysis.

2. Material and methods

2.1. Literature search

The systematic review and meta-analysis were performed according to the MOOSE (Research-Checklist) guidelines [8]. Search strategy is shown as PRISMA-flowchart [9] (Fig. 1). Two authors separately searched PubMed, Medline, Cochrane, CINAHL, and Web of Science for prospective studies assessing the association between NAFLD and CVD from inception through March 2016. Search was performed using various combinations of the following words: “NAFLD”, “Nonalcoholic steatohepatitis”, “NASH”, “Non-alcoholic Fatty Liver Disease”, and “Cardiovascular

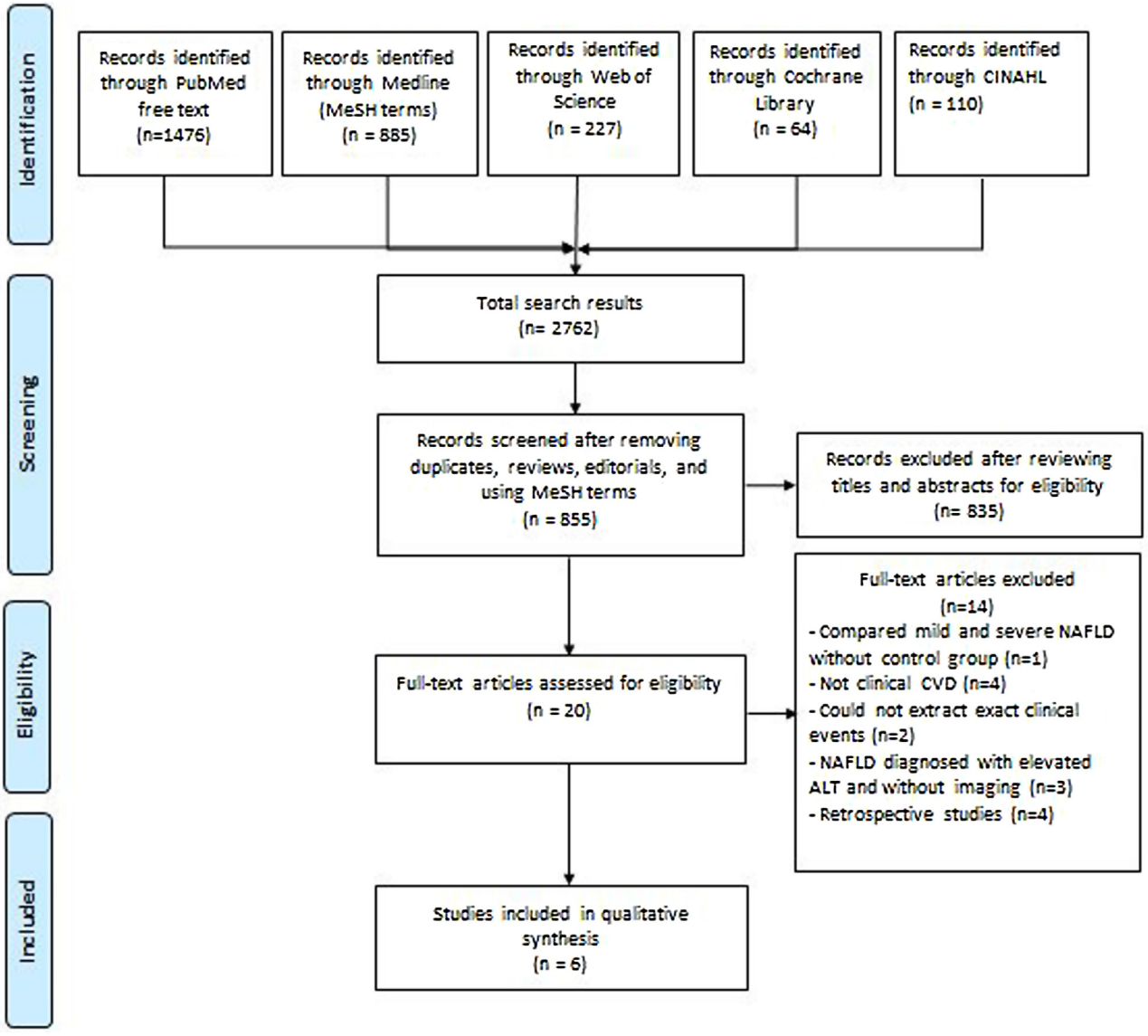

Fig. 1. PRISMA flowchart.

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