Int J Clin Exp Med 2017;10(4):6876-6882
www.ijcem.com /ISSN:1940-5901/IJCEM0044816

Original Article

Non-alcoholic fatty liver disease is associated with increased risk of hypertension and prehypertension: a systematic review and meta-analysis

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Received November 22, 2016; Accepted February 13, 2017; Epub April 15, 2017; Published April 30, 2017

Abstract: Raising evidence suggested that Non-alcoholic fatty liver disease (NAFLD) is associated with increased risk of prevalent metabolic syndrome and cardiovascular diseases. However, data on the association between NAFLD and hypertension and pre-hypertension were not conclusive. In the current study, we aimed to investigate the association between NAFLD and the risk of hypertension and prehypertension. Electronic databases including PubMed, EMBASE, Clinical Trials and Cochrane Library were comprehensively searched (publication date up to Jan, 2016). Data were synthesized using inverse variance calculations in random-effect model. Egger's test was used to detect publication bias. Five observational studies were included in the current meta-analysis, consisting of 36,534 participants. Compared with individuals without NAFLD, those with NAFLD had an increased risk of hypertension and prehypertension, pooled OR: 1.30; 95% CI: 1.14-1.47. There was evidence for heterogeneity among the five included studies (I^2=65.6%, $P < 0.05$). Our study demonstrated that NAFLD is a risk factor for hypertension and prehypertension. It is recommended that clinicians carefully monitor the blood pressure of patients with NAFLD.

Keywords: Non-alcoholic fatty liver disease, hypertension, risk factor

Introduction

Hypertension is one of the most common cardiovascular diseases (CVD) with increasing prevalence around the world, which is possibly driven by industrialization, urbanization and lifestyle changes of the modern society [1]. A population-based study from the United States reported that, NAFLD is the leading cause of abnormal liver function and chronic liver disease among its residents and approximately one third of the adults in the country have abnormal fat deposition in liver [2]. Moreover, NAFLD has been considered as a pathological change of the liver which could be a risk factor for CVD and metabolic syndrome [3]. As an important component of the metabolic syndrome, hypertension is prevalent in patients with NAFLD [4, 5]. The development of NAFLD is associated with key components of the metabolic syndrome both in adults and children. Individuals with NAFLD typically have greater levels of blood pressure, body mass index (BMI), waist circumference, and insulin resistance [6]. Thus, NAFLD promotes not only the development of severe liver diseases but also the increase of blood pressure.

Epidemiological studies reported that NAFLD is associated with hypertension or prehypertension among different kinds of population in various regions [7-11]. In the current meta-analysis, we aimed to evaluate the influence of NAFLD on blood pressure and providing meaningful guidance for the management of patients with certain disease.

Material and methods

Search strategy

We performed a comprehensive literature search through four electronic databases, including PubMed, EMBASE, Clinical Trials (https://www.clinicaltrials.gov/) and Cochrane Library (publication date up to Jan 1, 2016). "Nonalcoholic fatty liver disease", "hyperten-

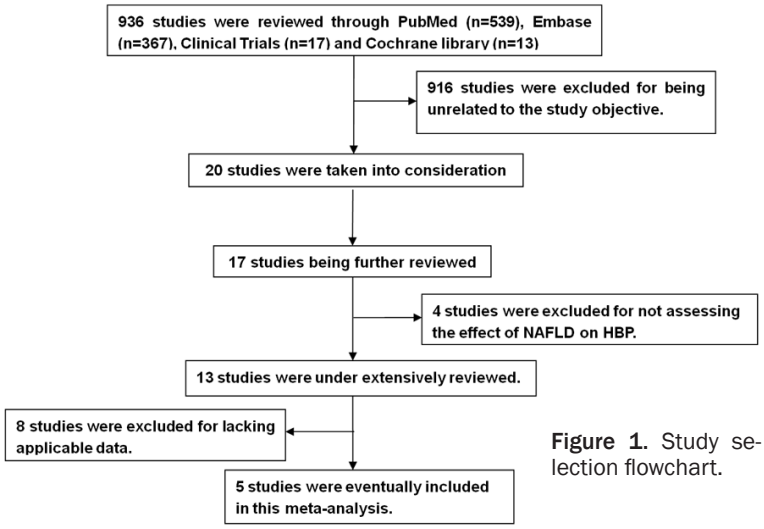

Figure 1. Study selection flowchart.

sion" and "high blood pressure" were used as keywords. Study species were restricted to "Humans". The search details were as follows: ("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 (("hypertension" [MeSH Terms] OR "hypertension" [All Fields]) OR ("hypertension" [MeSH Terms] OR "hypertension" [All Fields]) OR ("high "[All Fields] AND "blood" [All Fields] AND "pressure" [All Fields]) OR "high blood pressure" [All Fields])) AND "humans" [MeSH Terms]. All the searching process was conducted manually.

Study selection

A total of 936 items were found in the literature searching. The inclusion criteria of this meta-analysis are: 1) Data on the association between NAFLD and hypertension or prehypertension should be provided; 2) The diagnosis of NAFLD should be confirmed by qualified medical examinations (including ultrasound examination, evaluation of alcohol consumption). The definition of hypertension is systolic blood pressure (SBP) ≥ 140 mmHg or dystonic blood pressure (DBP) ≥ 90 mmHg or mean 24-h SBP ≥ 135 mmHg or DBP ≥ 85 mmHg or reported disease history. Prehypertension is defined as SBP of 120-139 mmHg or DBP of 80-89 mmHg (blood pressure within this range were also considered as prehypertension); 3) Study population should not include patients with positive serologic marker for hepatitis B surface antigen or hepatitis C virus antibody, alcohol intake of ≥ 20 g/day, a past history of a malignancy; 4) Sufficient data to calculate effect size was available and were expressed in a meaningful manner: hazard ratio (HR), risk ratio (RR) or odds ratio (OR). There were no restrictions on age, gender and racial of the patients. Finally, five studies were included in the data synthesis (**Figure 1**). Two authors independently retrieved all potentially eligible publications.

Data extraction

Detailed information of the five included studies was extracted, including first author, publication year, region, sample size, age of participants, state of NAFLD, state of blood pressure, effect size (HR/RR/OR; 95% CI), study type and period, adjusted factors. These data were presented in a structured table (**Table 1**). Data collection was performed by two investigators independently. Controversy was settled by discussion or consulting to a third researcher.

Statistical synthesis

In the present study, OR was assumed to be an effective risk evaluation. Forest plots were used to compare results between studies. The pooled OR was derived from the averaging per-study natural logarithmic HRs/ORs/RRs weighted by the inverses of their variances. We applied the DerSimonian and Laird random-effects model to incorporate between-study variability and to calculate the pooled effect estimates [12]. All the effect size values pooled in the analysis were the most adjusted ones if available. Heterogeneity among the five included studies was assessed by the I^2 statistic, which quantifies the percentage of total variation across studies that is due to heterogeneity rather than chance [13]. Publication bias was estimated through visually examining a funnel plot and performing the Egger's test. A two-tailed P value < 0.05 was defined as statistical significant of the results in the current study. All the data analyses were performed using Stata version 12.0 (Stata Corp, College Station, Texas).

Table 1. Basic characteristics of the included studies

Study	Region	Sample Size	Age (years)	Status of NAFLD	Blood Pressure	HR/RR/OR (95% CI)	Study Type and Period	Adjusted Factors
Jae-Hong Ryoo 2014	Korean	11350	Adults 41.4±5.8 Mean ± (SD)	Mild (Liver fat 63.7%-70.3%)	Pre-HBP (SBP of 120-139 mmHg or DBP of 80-89 mmHg)	1.18 (1.07-1.31)	Prospective cohort study 2005-2010	Age, HDL-cholesterol, log (hsCRP), serum creatinine, recent smoking status, regular exercise, MetS and diabetes mellitus.
				Moderate to Severe (Liver fat >70.3%)	Pre-HBP	1.62 (1.21-2.17)		
Jae-Hong Ryoo 2014 (J Gastroenterol Hepatol)	Korean	22090	Adults 42.1±(6.8) Mean ± (SD)	Mild (Liver fat 63.7%-70.3%)	HBP (SBP>140 mmHg or DBP>90 mmHg)	1.07 (1.00-1.15)	Prospective cohort study 2005-2010	Age, BMI, triglyceride, serum creatinine, AST, ALT, GGT, recent smoking status, regular exercise and diabetes mellitus
				Moderate to Severe (Liver fat >70.3%)	HBP	1.14 (1.00-1.30)		
Alejandro Lopez-Suarez 2011	France	454	Adults 50-75 (Range)	Ultrasound-diagnosed NAFLD	HBP (SBP>140 mmHg or DBP>90 mmHg or mean 24-h SBP≥135 mmHg or DBP≥85 mmHg)	1.71 (1.10-2.65)	Cross-sectional study 2006	Age, sex, and coverable with P less than 0.250 in bivariate analysis
					High normal SBP (130-139 mmHg)	2.13 (1.08-4.20)		
					High normal DBP (85-89 mmHg)	1.32 (0.72-2.43)		
Ren-Nan Feng 2014	China	1779	Adults 20-70 (Range)	NAFLD (diagnosed by formulation from Chinese National Workshop on Fatty Liver Disease in 2010)	HBP (BP>140/90 mmHg or with disease history)	1.49 (1.10-2.03)	Cross-sectional study 2012-2013	Age, sex, body mass index, smoking, alcohol consumption and physical activities
Jun-Fen Fu 2011	China	861	Children 6-16 (Range)	Fatty liver in ultrasound and normal transaminases	HBP (BP>140/90 mmHg or with disease history)	2.87 (1.29-6.37)	Clinical patients collection 2004-2009	NA
				Fatty liver in ultrasound and elevated transaminases		2.18 (1.27-3.75)		

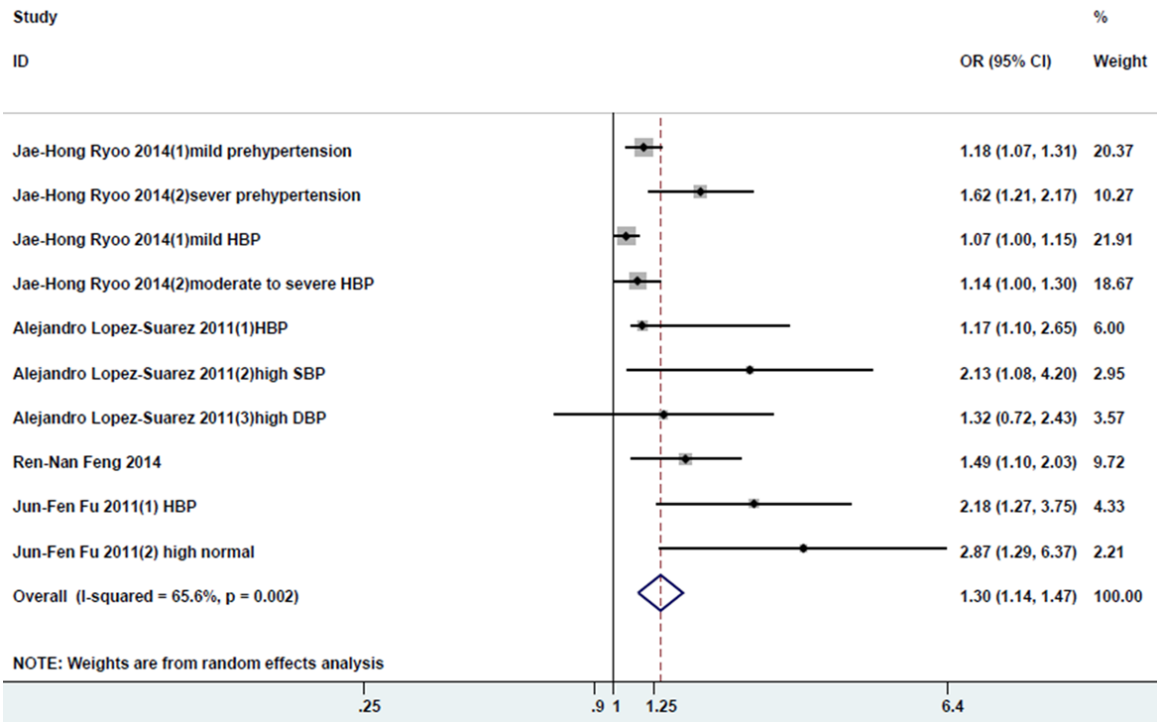

Figure 2. Forrest plot for meta-analysis of the risk of hypertension and prehypertension associated with development of NAFLD. Square indicates the effect size of each study which size is shown by weights. The length of the horizontal lines represents the 95% CI. The diamond indicates the pooled estimate of odds ratio (OR) and 95% confidence interval (95% CI). I-squared =65.6%.

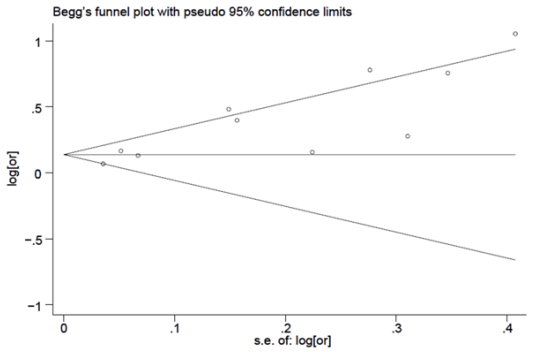

Figure 3. Detection of publication bias among the five included studies using Begg's funnel plot. Circles represent the standardized effects of the five studies which sizes are shown by weights. *P*=0.001.

Results

Study characteristics

Finally, five observational studies were included in the current meta-analysis, consisting of 36,534 participants. The included studies including two prospective studies [7, 8], two cross-sectional studies [9, 10] and one study based on clinical patients collection [11]. The included studies were conducted in Korean [7, 8], China [10, 11], and France [9]. The sample sizes of these studies various from 155 to 220 90.

Four studies were conducted among adults [7-10] and one study was conducted in minors [11]. Two of the included studies, both conducted by Ryoo, et al categorized the patients into two groups depending on liver fat percentage: 1) mild NAFLD; 2) moderate to severe NAFLD [7, 8]. Fu, et al divided their study subjects into two groups according to the level of transaminases. They found that patients with elevated level of transaminases related to minor increased risk of hypertension compared to patients with normal transaminases level [11]. The study conducted by Alejandro and colleges from France, sorted there patients into three groups according to different state of blood pressure and found that NAFLD exerted the strongest effect on the risk of having high normal systolic blood pressure [9]. Within the five studies which provided available infor-

mation on adjusted factors, most of them adjusted the confounders including age, gender, and recent smoking status.

Results of data synthesis

In the current study, NAFLD was associated with an increased risk of hypertension and prehypertension (pooled OR, 95% CI: 1.30, 1.14-1.47) (**Figure 2**). The increased risk of developing hypertension and prehypertension among patients with NAFLD was 30% (95% CI: 14% to 47%) in the current meta-analysis, not as various as previously reported (from 7% to 187%). Significant heterogeneity among the five included studies was detected (I^2=65.6%, *P*=0.002). In addition, we performed Begg's test to detect the publication bias among these five studies. There was evidence for the presence of publication bias (*P*=0.001) (**Figure 3**).

Discussion

The novel finding of our study is that NAFLD can increase 30% risk of having hypertension and prehypertension. To our knowledge, this is the first meta-analysis addressing this issue. Further large-scale prospective studies are needed to confirm this association and identifying related mechanisms.

NAFLD is one of the common hepatic disorders within creasing prevalence in China, which is mainly driven by the prevailing unhealthy life style [14]. Patients with NAFLD are at higher risk of having elevated blood pressure and experiencing increased overall mortality and liver-related mortality [15]. NAFLD has been considered as a benign and non-invasive condition. However, raising evidence showed that NAFLD is a crucial risk factor for metabolic and cardiovascular diseases [3-5]. A notable proportion of patients developed metabolic problems only a few years after the diagnosis of NAFLD [5]. Basically, NAFLD is mainly prevalent among middle-aged and elderly individuals and being accompanied with dyslipidemia, abnormal liver function tests, and high prevalence of type 2 diabetes [16]. These features make NAFLD a complicated metabolic disorder which would add unfavorable burden on the management of cardiovascular diseases including hypertension.

The potential mechanisms linking this association are not conclusive yet. A cohort study from Finland reported that high ambulatory blood pressure values were associated with increased risk of prevalent NAFLD in middle-aged adults. More importantly, coexistence of liver fat accumulation and high blood pressure would potentiate the risk for cardiovascular disease [17]. In patients with NAFLD, mild and severe portal inflammation were correlated with the prevalence of hypertension, diabetes, and increased BMI [18]. However, other factors including age, presence of diabetes, obesity and hypertension were not associated with mild and severe portal inflammation in patients with alcoholic fatty liver disease [18]. The above evidence indicated that NAFLD is more relevant to metabolic disorders than alcoholic fatty liver disease did. The activation of the innate immune system and release of pro-inflammatory cytokines from portal tract inflammatory cells might be the cause for the development of hypertension among patients with NAFLD [19]. Moreover, it was reported that there is significant impairment on systolic and diastolic function of the heart in the non-diabetic and normotensive NAFLD patients compared to patients without NFALD. The impairment on systolic and diastolic function might be caused by the cumulative effect of increased level of weight, insulin resistance, and blood pressure [20]. In addition, left ventricular mass was greater in patients with NAFLD, and the statistical significant difference was observed in those patients with more severe liver steatosis [21]. Given that, left ventricular hypertrophy is a major determinant of diastolic disorders in hypertensive patients, NAFLD might play a role in the pathogenesis of hypertension [22].

Furthermore, NAFLD had been reported to be associated with arterial stiffness among different populations [22-24]. According to a case-control study, patients with NAFLD had significantly higher prevalence of increased carotid intima-media thickness (CIMT) compared to healthy individuals. Those accompanied with hypertension had even much higher prevalence of thick CIMT [23]. These findings indicated that the onset of hypertension in patients with NAFLD would promote the development of arterial stiffness and related cardiovascular diseases.

Several limitations must be claimed for the current study. First, the limited number of included studies prevented us doing further

classification on the different state of NAFLD. Second, the participants recruited in the five included studies various in several aspects including age, gender and race, which might have an influence on the results. Given that both of NAFLD and hypertension did not show obvious difference between age, gender and race, these factors may not be major confounders for the current meta-analysis.

To conclude, NAFLD is a risk factor for hypertension and prehypertension, we recommend that clinicians carefully manage the blood pressure in individuals with NAFLD.

Disclosure of conflict of interest

None.

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