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Research Article

# Bidirectional association between nonalcoholic fatty liver disease and hypertension from the Dongfeng-Tongji cohort study

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## Abstract

The relation between nonalcoholic fatty liver disease (NAFLD) and hypertension is not fully understood. To examine the effect of the change in NAFLD status on the risk of incident hypertension, and vice versa, 6704 eligible hypertension-free subjects and 9328 NAFLD-free subjects from the Dongfeng-Tongji cohort study at baseline were enrolled in the study. Among the hypertension-free subjects, development and persistence of NAFLD were associated with an increased odds ratio (OR) for incident hypertension (OR: 1.49, 95% confidence interval [CI]: 1.26–1.76, $P < .0001$; OR: 1.50, 95% CI: 1.27–1.78, $P < .0001$). However, the resolution of NAFLD was not a risk factor for incident hypertension. Among the NAFLD-free subjects, the risk of new-emerging NAFLD was robust for hypertension status both in no-yes (OR: 1.45, CI: 1.23–1.71) and yes-yes (OR: 1.61, CI: 1.35–1.92). Moreover, stratified analysis by diabetes and overweight/obese for the risk of incident NAFLD showed that incident hypertension (no-yes) and persistent hypertension (yes-yes) were associated with risk of incident NAFLD in subjects without diabetes or overweight/obesity. In the overweight/obese participants, persistent hypertension (yes-yes) was a risk factor for incident NAFLD (OR: 1.29, 95% CI: 1.01–1.64, $P = .0387$). Conclusively, incidence and persistence of NAFLD are associated with increased risk of hypertension, and vice versa. J Am Soc Hypertens 2018;■(■):1–11. © 2018 Published by Elsevier Inc. on behalf of American Heart Association.

*Keywords:* Bidirectional association; blood pressure controlling; hypertension; nonalcoholic fatty liver disease.

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## Introduction

Emerging evidence has shown a clear clustering of hypertension among patients with nonalcoholic fatty liver disease (NAFLD) and vice versa.[1,2] Approximately 50% of hypertensive patients have NAFLD,[3] and in contrast, the prevalence rates of fatty liver disease (FLD) among hypertensive patients were 30%–56%.[4,5] Numerous studies have investigated the association between FLD and hypertension.[5–7] Sung et al[8] exhibited a dramatic increased odds ratio (OR) of 1.36 for incident hypertension associated with incident FLD after 5 years' follow-up, but the patients with FLD were collected without definition of causes, such as drugs known to be associated with FLD. Nevertheless, NAFLD, alcoholic FLD, and viruses-related FLD trigger hypertension by different pathophysiological mechanisms, and hypertension in turn initiates FLD through interaction with individual factors.[4,9,10]

On the other hand, less attention has been given to the investigation of whether NAFLD is an independent risk factor for hypertension. Based on a cross-sectional examination from 5362 healthy middle-aged Brazilian,[11] controlling blood pressure (BP) among nonobese hypertensive patients possessed a benefit in preventing or limiting NAFLD, but the participants with excessive alcohol consumption was not described to exclude. In addition, little meritorious cohort work was available focusing on whether the change in hypertension status (either development of new NAFLD or BP control of existing hypertension) modified risk of incident NAFLD.

Although growing evidence suggested that the NAFLD-hypertension relation is bidirectional,[6,7,12] few studies simultaneously investigated the bidirectional association between NAFLD and hypertension in a prospecting setting, especially with large sample size focusing on new, resolute, and persisting cases. Moreover, limited studies observed whether the resolution of NAFLD have an impact on the onset of hypertension and whether the effective control of BP in patients with hypertension was protective against the onset of NAFLD. Therefore, we proposed an assumption of reciprocal causality according to the mutual positive association of both conditions. The bidirectional causal links were analyzed and evaluated based on the Dongfeng-Tongji cohort study with abundant information on demographic, physiological, and biochemical status.

## Materials and Methods

### *Study Population*

The Dongfeng-Tongji cohort study was initiated in 2008 among retired workers of Dongfeng Motor Corporation located in Shiyan City, Hubei, China. Between September 2008 and June 2010, 87% (n = 27,009 of 31,000) of invited retired employees responded to the study. The distributions of baseline variables were similar between the responders and the nonresponders in our cohort as previously described in detail.[13] The first follow-up information was collected from April to October in 2013. This study was approved by the Medical Ethic Committee of the School of Public Health, Tongji Medical College, and Dongfeng General Hospital, Dongfeng Motor Corporation. All participants provided written informed consent.

### *Data Collection and Covariables Measurement*

Trained interviewers administrated a semistructured questionnaire to obtain the baseline information including demographic information, socioeconomic status, family and personal disease histories, smoking status, alcohol use, and physical activity during a face-to-face interview. The physical examination was also conducted at the same time to collect baseline data on standing height, body weight, and waist circumference, which were measured in individuals with light indoor clothing and without shoes. Body mass index (BMI) was calculated as weight (kilograms)/standing height (square meters). Overweight and obesity were defined as having a BMI between 24.0 to 28.0 kg/m$^2$ and a BMI of $\geq$28.0 kg/m$^2$, respectively, according to the classifications for Asian populations.[14]

Other information including lifestyle features, history of disease, and medication use was also obtained from the questionnaire. In addition, measurement of blood lipids (total cholesterol [TC], triglycerides [TGs], high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol [LDL-c]), hepatic function (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and renal function (blood urea nitrogen [BUN], uric acid, and creatinine) were performed in hospital's laboratory based on the colorimetric analyses on an ARCHITECT ci8200 automatic analyzer (Abbott, USA). Fasting glucose was determined by an Aeroset automatic analyzer (Abbott Park, Green Oaks, IL). The complete blood constituents were measured by CELL-DYN 3700 from Abbott Laboratories of USA. Estimated glomerular filtration rate (eGFR) was computed according to the formula: eGFR (mL/min per 1.73 m$^2$) = 186 $\times$ (creatinine)$^{-1.154}$ $\times$ (Age)$^{-0.203}$ $\times$ (0.742 if female) $\times$ 1.233.[15,16] As a score of liver fibrosis, FIB-4 was calculated as age $\times$ AST (U/L)/(platelet count [ $\times$ 10$^9$/L] $\times$ $\sqrt{\text{ALT}\frac{\text{U}}{\text{L}}}$).[17]

### *Assessment of NAFLD*

NAFLD was defined as a fatty liver diagnosed using an Aplio XG ultrasound machine (TOSHIBA, Japan) performed by a unique independent specialist operator dedicated to abdominal ultrasound examinations. Hepatic steatosis was defined by the presence of at least 2 of 3 abnormal findings on abdominal ultrasonography: diffusely increased