Original Article

Association between non-alcoholic fatty liver disease and silent carotid plaque in Chinese aged population: a cross-sectional study

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Background: Non-alcoholic fatty liver disease (NAFLD) is a risk factor for carotid plaque in the general population; however, whether NAFLD is associated with carotid plaque in aged population remains unknown. This cross-sectional study was conducted to evaluate the association between NAFLD and carotid plaque in a Chinese aged population.

Methods: A total number of 12,990 Chinese aged adults (7,685 men and 5,305 women) were included. NAFLD was diagnosed based on the recommendation of Asia-Pacific Working Party on NAFLD and Chinese Association for the Study of Liver Disease and excessive alcohol consumption (weekly alcohol consumption ≤210 g in men and ≤140 g in women) was excluded. Carotid plaque was confirmed by ultrasonography. Potential confounders and biochemical findings were collected at baseline. Logistic regression model was employed to evaluate the association between NAFLD and carotid plaque.

Results: The prevalence of carotid plaque was significantly higher in aged participants with NAFLD than in those without NAFLD (22.4% *vs.* 16.3%, P<0.001). NAFLD is associated with carotid plaque [odd ratio (OR) =1.89, 95% confidence interval (CI): 1.59–2.24], after adjusting for age, gender, BMI, liver and kidney function, glucose level, lipid profiles, and white blood cell (WBC) count. The association between NAFLD and carotid plaque was attenuated when participants with elevated ALT (≥75 IU/L), a history of cardiovascular diseases (CVDs) and obesity were censored although the significant association remained.

Conclusions: NAFLD is associated with carotid plaque in Chinese aged population.

Keywords: Non-alcoholic fatty liver disease (NAFLD); carotid plaque; aged population; subclinical atherosclerosis

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Introduction

Non-alcoholic fatty liver disease (NAFLD) affects about one third of adults in both western countries and China (1,2). Although NAFLD is not a component of metabolic syndrome, existing evidence suggests a strong association between NAFLD and cardiovascular diseases (CVDs) (3). Carotid plaque is usually considered as a manifestation of subclinical atherosclerosis and can predict future cardiovascular events (4). Several studies have evaluated the association between NAFLD and subclinical atherosclerosis (5-17), but there is still controversy on this issue. Some studies (6,7,9,16), but not all (11,18), have revealed that NAFLD is an indicative index for carotid plaque, regardless of sample size, study design, degree of adjustment and

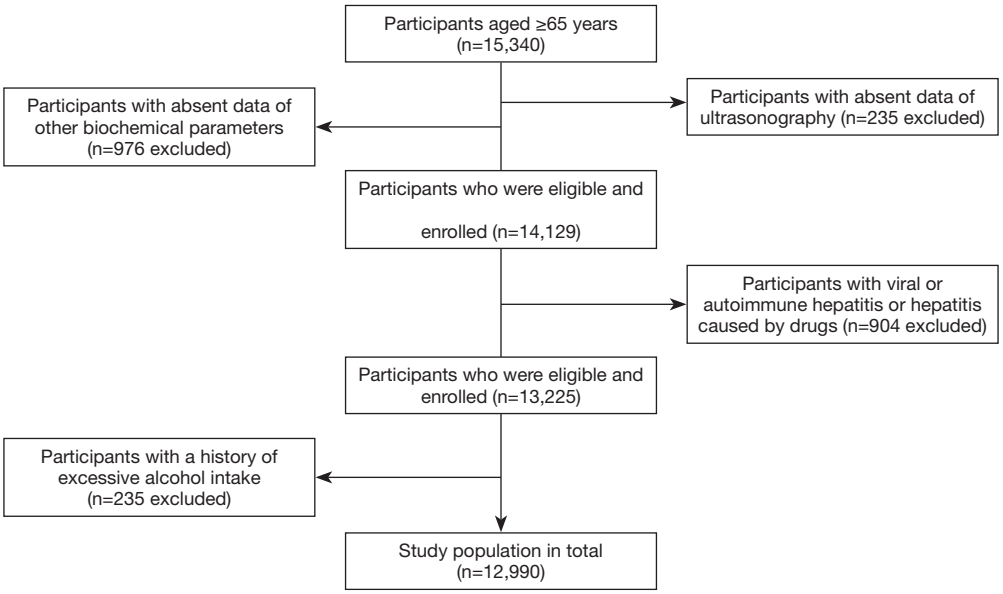

Figure 1 Flow chart of study population selection.

ethnicity. Another cross-sectional study involving 144 subjects showed that liver fat content was significantly higher in patients without plaque than in their counterparts (P=0.009) while the liver fat content was negatively associated with plaque (OR =0.94; 95% CI, 0.89–0.99) in multivariable analysis (19). Interestingly, few studies on the association between NAFLD and carotid plaque have focused on aged adults, who have high risks for carotid plaque and stroke (20,21).

Therefore, the present study was conducted to assess the association between NAFLD and carotid plaque in about 13,000 Chinese aged adults. Because carotid plaque is related to the elevated ALT levels (22), history of CVD (23) and obesity (24), we further conducted three sensitivity analyses to test the robustness of the association between NAFLD and carotid plaque.

Methods

Study population

All the Chinese aged participants (≥65 years) were recruited from the Health Examination Center, Ren Ji Hospital between January 2013 and October 2018. A total of 15,340 Chinese aged adults were included. After excluding participants with incomplete information (n=1,211), viral/autoimmune hepatitis (n=613), drug-induced hepatitis (n=291) or alcohol consumption (n=235), 12,990 (7,685 men and 5,305 women) Chinese aged adults were finally included for analysis (*Figure 1*). The study protocol was approved by the Ethical Committee of Ren Ji Hospital (2019-112).

Assessment of NAFLD

Abdominal ultrasonography was performed using a high-resolution topographic ultrasound system with a 3.5 MHz probe (ACUSON X300, Siemens, Germany) in all the participants after overnight fast. There is evidence showing that the abdominal ultrasonographic findings closely mirror the entity of hepatic steatosis change >20% (25), and ultrasound examination is an optimal tool for the longitudinal follow-up in the elderly (26). Participants were diagnosed with NAFLD based on the presence of two of following findings: (I) diffusely increased echogenicity in the liver as compared to the kidney; (II) echogenicity attenuation; (III) poor visualization of intrahepatic structures, but absence of excessive alcohol abuse (weekly alcohol consumption ≤210 g in men and ≤140 g in women) and other liver diseases, based on the commendation of the Asia-Pacific Working Party on NAFLD and Chinese Association for the Study of Liver Disease (27,28).

Assessment of carotid plaque

Carotid plaque was also confirmed by carotid

ultrasonography (Philips HDI 5000 ultrasound system equipped with a 7.5 MHz probe). Carotid ultrasonography is the primary noninvasive examination for the diagnosis and follow-up of internal carotid arteriosclerosis and carotid plaque (29). The carotid intima-media thickness (CIMT) was measured at about 1.5 cm away from the bifurcation of the common carotid artery. Carotid plaque was defined as a focal region with the thickness >1.5 mm as measured from the media adventitia interface to the lumen-intima interface or as the presence of focal wall thickening (at least 50% greater than that of the surrounding vessel wall) (30).

Assessment of other confounding factors

Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Body mass index (BMI) was calculated by body weight (kg) divided by the square of height (m^2). Obesity was defined as BMI ≥28.0 kg/m^2 based on the recommendation of Chinese Obesity Working Group (31). Blood pressure (BP) was measured using a mercury sphygmomanometer after at least 10-min rest. Information about liver function [alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (AKP), gamma-glutamyl transferase (γ-GT), total bilirubin (TBI), direct bilirubin (DBI)], kidney function [blood urea nitrogen (BUN), creatinine (Cr), and uric acid (UC)], fasting blood glucose (FBG), lipid profiles [total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C)], and white blood cell (WBC) was also collected based on the medical records. All participants completed a health questionnaire covering issues such as history of major diseases and alcohol consumption. The excessive alcohol consumption was defined as >210 g of alcohol per week in men and >140 g per week in women (32).

Statistical analysis

Statistical analysis was performed with SAS version 9.4. Continuous variables were compared with *t*-test and categorical variables with Chi-square test. The association between NAFLD and carotid plaque was assessed with the multivariate logistic regression analysis. One crude model (no adjustment) and two adjusting models were constructed: in *model 1*, analysis was done after adjustment for age (y) and sex; in *model 2*, analysis was done after adjustment for BMI (kg/m^2), ALT (IU/L), AST (IU/L), AKP (IU/L), γ-GT (IU/L), TBI (mmol/L), DBI (mmol/L), BUN (mmol/L), Cr (μmol/L), UC (μmol/L), TC (mmol/L), TG (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), FBG (mmol/L), and WBC (10^9/L). A value of two-sided P<0.05 was considered statistically significant.

We tested the interaction between NAFLD and sex, and age, with the relation to carotid plaque. To test the robustness of the results, we performed three sensitivity analyses: excluding participants with elevated serum ALT (≥75 U/L) (33), history of CVD (34), and obesity (BMI >28.0 kg/m^2) (31).

Results

There were 6,002 aged participants with NAFLD and 6,988 aged participants without NAFLD. The mean age was 70.8±6.1 years. NAFLD participants were more likely to have higher BMI, systolic blood pressure (SBP), glucose level, TG, LDL-C, serum ALT, AST and γ-GT than those without NAFLD (*Table 1*).

The prevalence of carotid plaque was 19.1% in the aged population. The prevalence of carotid plaque was significantly higher in NAFLD patients than in subjects without NAFLD (22.4% *vs.* 16.3%, P<0.001). As compared to participants without NAFLD, NAFLD participants were more likely to develop carotid plaque (89%) (OR =1.89; 95% CI: 1.59–2.24) after adjustment for age, sex, BMI, liver and kidney function, glucose level, lipid profiles, and WBC count (*Table 2*, *model 3*).

After excluding the participants with elevated ALT (≥75 U/L), a history of CVDs, and obesity (BMI > 28.0 kg/m^2), similar results were found (*Table 3*).

Discussion

In the present study, results showed NAFLD was associated with carotid plaque in 12,990 Chinese aged adults, after adjusting BMI, BP, fasting blood glucose, lipid profiles.

Similar findings have been confirmed in some studies on young adults (13,35). Participants with NAFLD had higher prevalence of subclinical atherosclerosis. In participants over 40 years, hepatic steatosis is also independently associated with the elevated CIMT after adjusting for age, gender, BMI, current smoking and regular exercise (36). Systematic reviews and meta-analysis have confirmed the strong association between hepatic steatosis and increased CIMT (9,16,37). In line with these findings in populations including adults and children (13,15-17,36,38-40), our study extended the positive correlation between NAFLD and

Table 1 Baseline characteristics of 12,990 Chinese aged participants

Indexes	Total	NAFLD (n=6,002)	non-NAFLD (n=6,988)	P
Age, y	70.8±6.1	70.4±5.6	71.2±6.5	<0.001
Male, n (%)	–	3,553 (59.2)	4,132 (59.1)	–
BMI, kg/m^2	24.6±3.2	26.1±2.8	23.3±2.9	<0.001
SBP, mmHg	141.5±18.9	143.5±18.0	139.8±19.5	<0.001
DBP, mmHg	77.6±10.8	78.9±10.6	76.5±10.9	0.01
FBG, mmol/L	5.8±1.5	6.1±1.6	5.6±1.3	<0.001
TC, mmol/L	5.1±1.0	5.1±1.0	5.0±1.0	0.38
TG, mmol/L	1.6±1.0	1.9±1.2	1.3±0.7	<0.001
LDL-C, mmol/L	3.0±0.8	3.1±0.8	2.9±0.8	0.56
HDL-C, mmol/L	1.4±0.4	1.2±0.3	1.5±0.4	<0. 001
ALT, IU/L	20.1±13.3	22.9±15.9	17.7±10.1	<0.001
AST, U/L	21.8±10.7	22.2±13.1	21.4±8.1	<0.001
AKP, U/L	77.6±23.8	77.7±21.7	77.5±25.5	<0.001
γ-GT, U/L	28.8±28.3	32.6±29.9	25.4±26.3	<0.001
DBI, μmol/L	4.1±2.4	4.0±2.1	4.2±2.6	<0.001
BUN, mmol/L	5.5±1.5	5.5±1.4	5.6±1.6	<0.001
Cr, μmol/L	77.4±24.2	77.7±26.0	77.1±22.4	<0.001
Uric acid, μmol/L	334.6±80.9	352.8±79.8	324.6±79.6	0.85
WBC, ×10^9/L	–	6.5±1.6	5.9±1.5	0.20
Carotid plaque				
Presence		1,342	1,142	<0.001
Absence		46,600	5,846	–

AKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; DBI, direct bilirubin; DBP, diastolic pressure; FBG ,fasting blood glucose; HDL, high density lipoprotein ;LDL-C, low density lipoprotein cholesterol; SBP, systolic pressure; TC, total cholesterol; TG, triglyceride; WBC, white blood cell; γ-GT, γ-glutamyl transpeptidase.

Table 2 Association between NAFLD and carotid plaque in 12,990 Chinese aged participants

Model	Participants		P
	NAFLD	non-NAFLD	
Sample number	6,988	6,002	–
Case of carotid plaque	1,142	1,342	–
Crude	1 (ref)	1.47 (1.35–1.61)	<0.001
Model 1	1 (ref)	1.5 (1.37–1.64)	<0.001
Model 2	1 (ref)	1.89 (1.59–2.24)	<0.001

(I) Crude model: no adjustment; (II) Model 1: adjustment for age (y) and sex; (III) Model 2: adjusted for age (y) and sex, BMI (kg/m^2), ALT (IU/L), AST (IU/L), AKP (IU/L), γ-GT (IU/L), TBI (mmol/L), DBI (mmol/L), BUN (mmol/L), Cr (μmol/L), UC (μmol/L), TC (mmol/L), TG (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), FBG (mmol/L), and WBC (10^9/L).

Table 3 Association between NAFLD and carotid plaque (sensitivity analysis)

Sensitivity	NAFLD	non-NAFLD	P
Sensitivity 1	–	–	–
Sample number	5,924	6,961	–
Case of carotid plaque	1,331	1,139	–
OR	1 (ref)	1.87 (1.52–2.23)	<0.001
Sensitivity 2	–	–	–
Sample number	3,618	4,783	–
Case of carotid plaque	919	751	–
OR	1 (ref)	2.22 (1.78–2.77)	<0.001
Sensitivity 3	–	–	–
Sample number	4,682	6,619	–
Case of carotid plaque	1,102	1,066	–
OR	1 (ref)	1.95 (1.62–2.34)	<0.001

(I) All the analyses were done after adjustment for age (y) and sex, BMI (kg/m^2), ALT (IU/L), AST (IU/L), AKP (IU/L), γ-GT (IU/L), TBI (mmol/L), DBI (mmol/L), BUN (mmol/L), Cr (μmol/L), UC (μmol/L), TC (mmol/L), TG (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), FBG (mmol/L), and WBC (10^9/L). (II) Sensitivity analysis 1: excluding participants whose ALT 75 U/L (n=105). (III) Sensitivity analysis 2: excluding participants with a history of cardiovascular diseases (n=4,589). (IV) Sensitivity analysis 3: excluding participants with obesity (BMI: >28.0 kg/m^2) (n=1,689).

carotid plaque to the elderly population. The absence of significant association between NAFLD and carotid plaque in other studies (11,18,19) might be related to the different diagnostic methods for NAFLD, the specific populations, the use of low frequency linear ultrasound probes, small sample size and the different ethnicity.

The most important finding in our study was that the risk of preclinical atherosclerosis persisted or even increased in asymptomatic individuals with NAFLD. Higher ALT level is also associated with increased subclinical atherosclerosis (37). In addition, elevated serum ALT level suggests more severe steatohepatitis. Thus, participants with ALT higher than 75 U/L were excluded for further analysis, and results showed the relative risk of carotid plaque detection persisted in NAFLD patients. This indicates that mild NAFLD is sensitive enough to screen out carotid plaque. Obesity is an accepted risk factor for preclinical atherosclerosis, and several studies that questioned the positive correlation between NAFLD and carotid plaque may just be a consequence of the association between obesity and atherosclerosis (11,35). Thus, obese participants were excluded for further analysis. Unexpectedly, in non-obese population, the hepatic steatosis was more closely associated with carotid plaque (OR =1.95). This unexpected higher risk was also present in NAFLD participants without prior history of CVD (OR =2.22). These results justify a necessity to screen for silent carotid plaques in the old NAFLD patients. Kang *et al.* (41) found that NAFLD-associated adjusted odds ratio of carotid plaque was 1.58 (95% CI: 1.31–1.86) without MetS and 1.54 (95% CI: 0.51–4.6) with MetS in outpatients without diabetes, which supported our findings. In another study, the association between NAFLD and carotid plaque was more prominent in young adults without MetS than in old adults or in those with MetS (7). These results, together with our findings, suggest that, in asymptomatic individuals, the carotid plaque may be more prevalent than in high risk populations. Thus, the screening for carotid plaque in all NAFLD individuals will be beneficial for the assessment of future atherosclerotic complications.

The large sample size and inclusion of multiple biochemical indicators were the advantages of present study. However, several limitations should be addressed. First, as a cross-sectional study, the causative association between NAFLD and carotid plaque could not be determined. Second, the drugs (such as aspirin and statin) that were reported to be associated with carotid plaque were not excluded (42) although participants with a history

of CVD were excluded for further analysis. Finally, all the participants were recruited from a single center, which could not represent the general population. Thus, the results must be interpreted with caution. Further community-based prospective studies are needed to confirm our results.

In conclusion, our study indicates NAFLD is associated with carotid plaque in Chinese aged population.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Ethical Committee of Ren Ji Hospital (2019-112).

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