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# Factors Significantly Associated With the Increased Prevalence of Carotid Atherosclerosis in a Northeast Chinese Middle-aged and Elderly Population

## *A Cross-sectional Study*

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**Abstract:** Carotid atherosclerosis is associated with many serious cardiovascular diseases; hence, it is necessary to identify factors related to its occurrence in order to develop preventive and therapeutic strategies. This study was conducted to identify risk factors associated with carotid atherosclerosis among the population residing in Northeast China.

This epidemiological survey was conducted in a representative group of relatively healthy community residents. All participants answered questions about their medical histories and underwent physical examination, blood biochemical analysis, and ultrasonography examinations of their necks and abdomens. The prevalence rates of carotid atherosclerosis under different factors and conditions were then analyzed.

The results of this study showed that age, gender, and diabetes significantly affected the prevalence of carotid atherosclerosis in this Northeast Chinese population. In addition, gender-based subgroup analysis revealed additional factors correlated with the prevalence of carotid atherosclerosis in men or women, although their correlations were not significant in the overall population. While high serum TC and LDL-C levels were risk factors for carotid atherosclerosis in men, it showed no clear correlation with the prevalence of carotid atherosclerosis in women. In contrast, the prevalence of carotid atherosclerosis in female participants with high serum TG level, hypertension, obesity and nonalcoholic fatty liver disease were higher than that of the control population, a trend not observed in male participants.

Older age, male sex, and diabetes were independently associated with increased risk of carotid atherosclerosis in Northeast China. These

findings could lead to improved screening for carotid atherosclerosis for better disease management.

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**Abbreviations:** CA = carotid atherosclerosis, IFG = impaired fasting glycaemia, IGT = impaired glucose tolerance, NAFLD = nonalcoholic fatty liver disease.

## INTRODUCTION

Although great progress has been made in understanding the cause, diagnosis, treatment, and other aspects of cardiovascular diseases, the current situation is far from satisfactory,<sup>1</sup> and cardiovascular diseases remain a leading cause of death worldwide.<sup>2</sup> The neck vasculopathy carotid atherosclerosis (CA) is strongly associated with multiple major adverse cardiovascular events.<sup>3,4</sup> One study reported that approximately 80% of anterior circulation strokes were ischemic, and at least 20% of ischemic strokes were caused by CA.<sup>5</sup> Moreover, atherosclerotic lesions in the carotid or internal carotid arteries are usually signs of future coronary artery disease. This predictive ability has a wide range of potential applications among both asymptomatic individuals with vasculopathic risk factors and patients with symptoms of arterial diseases.<sup>6,7</sup>

CA is associated with many cardiovascular diseases that threaten human life and health; hence, it is necessary to identify factors relevant to the occurrence of CA in order to develop preventive and therapeutic strategies. Some epidemiological studies have investigated the risk factors of CA.<sup>8–10</sup> However, only a few epidemiological studies have researched Chinese populations, and data on the population from Northeast China in particular is limited. The climate and eating habits in Northeast China vary widely from those in South China: it is much colder, with more lipid intake in daily meals. The main objective of this study was to conduct an epidemiological survey to evaluate the risk factors associated with CA among the population residing in Northeast China.

## METHODS

### Study Population

In order to identify factors related to the occurrence of CA, an epidemiological study was performed on a representative group of male and female residents of Shenyang, Liaoning Province, China. Community residents were included in our study through a multistage, stratified, random, and cluster-sampling scheme. Individuals with excessive alcohol consumption ( $\geq 40$  g/d for men,  $\geq 20$  g/d for women) were excluded.

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Individuals with severe hepatitis B, hepatitis C, or other liver diseases were also excluded from this study. Other exclusion factors included participants with diseases that could affect their metabolic state or diseases that made the individuals unsuitable for this study, such as mental illness, severe cardiac or pulmonary insufficiency, and cancer. Among 533 individuals invited to participate, 474 (88.9%) completed the study.

This study was approved by the Ethics Committee of China Medical University, and all its procedures followed the ethical standards of the Ethics Committee of China Medical University. All participants were informed about the objectives, significance, medical procedures, and the plan for protecting the privacy of their personal information before providing written consent.

## Data Collection and Measurement

All participants answered questions about their medical histories and underwent physical examinations, blood biochemical analyses, and ultrasonography examinations of their necks and abdomens. Demographic characteristics and lifestyle risk factors were obtained through a standardized questionnaire completed by researchers during in-person interviews. A central guidance committee performed quality control assessment of the questionnaires to ensure that the data collection processes met the pre-existing standards.

Waistline measurements were performed using the standard method to the nearest 0.1 cm. Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as the body weight (kg) divided by the square of the height (m).

Blood pressures were measured three times at 2-minute intervals after the participants had rested for at least 5 minutes, with the average of the three measurements used in subsequent statistical analysis. Participants were asked to avoid consuming caffeinated beverages and strenuous exercise at least 30 minutes before the measurements, which were performed in a seated position with arms at heart height.

Blood sample collection, processing, and testing at a certified central laboratory for levels of fasting plasma glucose (FPG), plasma glucose 2 hours after glucose-load, and fasting plasma insulin (FPI), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were performed according to standard procedures.

The carotid artery and liver ultrasonography examinations were performed separately by experienced neck and abdominal radiologists, respectively, who were blinded to participants' clinical and biochemical characteristics. All diagnostic procedures were conducted following standardized diagnostic protocols.<sup>11,12</sup>

## Definitions

Hypertension was assessed as the average value of three blood pressure measurements for each participant and defined as systolic blood pressure (SBP)  $\geq 140$  mm Hg, and/or diastolic blood pressure (DBP)  $\geq 90$  mm Hg, and/or administration of antihypertensive drugs.<sup>13</sup> The reference ranges for the blood biochemical indexes measured in this study were: TC  $< 5.18$  mmol/L; TG  $< 1.7$  mmol/L; HDL-C  $\geq 1.04$  mmol/L; LDL-C  $< 3.37$  mmol/L. These ranges were applicable to both adult men and women.<sup>14</sup> Obesity was defined as BMI  $\geq 28$  kg/m<sup>2</sup>.<sup>15</sup> Diabetes was defined as venous fasting plasma glucose levels  $\geq 7.0$  mmol/L, plasma glucose levels 2 hours after

glucose-load  $\geq 11.1$  mmol/L, or having received diabetes intervention treatments; impaired glucose tolerance (IGT) was defined as venous fasting plasma glucose levels  $< 7.0$  mmol/L and plasma glucose levels 2 hours after glucose-load  $\geq 7.8$  and  $< 11.1$  mmol/L; and impaired fasting glycaemia (IFG) was defined as venous fasting plasma glucose levels  $\geq 6.1$  and  $< 7.0$  mmol/L and plasma glucose levels 2 hours after glucose-load  $< 7.8$  mmol/L.<sup>16</sup> A current smoker was defined as anyone who currently smokes any tobacco product on some or all days.<sup>17</sup> Similarly, a current drinker was defined as anyone who currently drinks any alcohol product on some or all days; however, alcohol intake was limited to the equivalent of  $< 40$  g/d for males and 20 g/d for females, in order to distinguish patients with alcoholic liver disease.

## Statistical Analysis

The Kolmogorov–Smirnov test was used to assess the normality of the data distribution. Based on these results, normally distributed continuous variables were presented as means  $\pm$  standard deviations; those not normally distributed were presented as medians and quartile distances. Independent sample *t*-tests and Mann–Whitney rank sum tests were used to compare two sets of normally distributed continuous variables and two sets of non-normally distributed continuous variables, respectively.

Categorical variables were presented as prevalence rates (percentages), while intergroup comparison of categorical variables was performed using chi-square tests. Odds ratios (ORs) and 95% confidence intervals (CIs) of dichotomous variables were calculated. Missing data were addressed by excluding participants from analysis who did not have the data point of interest recorded. Adjustments were made for the following variables: smoking status, alcohol consumption (units per day), and medical history of diabetes by questionnaire. *P* values  $< 0.05$  were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY).

## RESULTS

### General Characteristics of the Participating Population

A total of 533 individuals were enrolled in this study; however, 59 were excluded due to not meeting the inclusion criteria or incomplete data. Therefore, 474 individuals were included in the analyses, including 231 men and 243 women ranging from 40 to 70 years of age. Based on their carotid artery ultrasonography examination results, the participants were divided into either the CA or the non-CA groups. Detailed results of the comparative analysis between the two groups are shown in Table 1. The prevalence of CA was significantly higher in male participants than in female participants. In addition, the prevalence of CA was significantly higher in the smoking, alcohol-consuming, hypertensive, nonalcoholic fatty liver disease (NAFLD), IGT, and diabetic populations than in the nonsmoking, nonalcohol-consuming, nonhypertensive, non-NAFLD, non-IGT, and nondiabetic populations, respectively (all *P* values  $< 0.05$ ). Moreover, age, SBP, DBP, FPG, plasma glucose 2 hours after glucose load, HOMA-IR, BMI, TC, TG, and LDL-C were significantly higher in the CA group than in the non-CA group, while HDL-C level was significantly lower in the CA group than in the non-CA group. Nevertheless, there was no statistically significant difference in the FPI level between the two groups. Moreover, the prevalence of CA in

**TABLE 1.** General Characteristics of the Study Population. Values are Expressed as Mean ± SD, Median (Interquartile Range), or n (%). P Values were Obtained by the t-Test, the Mann–Whitney U Test, or the  $\chi^2$  Test, respectively

Variable	Carotid Atherosclerosis (n = 191)	Noncarotid Atherosclerosis (n = 283)	P
Age, years	57.0 (52.0–62.0)	52.0 (47.0–56.0)	<0.001
Gender			<0.001
Male (n = 231)	124 (53.7%)	107 (46.3%)	
Female (n = 243)	67 (27.6%)	176 (72.4%)	
SBP, mm Hg	143.33 (130.00–161.67)	130.00 (120.00–143.33)	<0.001
DBP, mm Hg	90.00 (81.67–100.00)	86.67 (80.00–96.00)	<0.001
FPG, mmol/L	5.72 (5.27–6.90)	5.31 (5.04–5.82)	<0.001
2 h PG, mmol/L	7.82 (5.90–11.73)	6.03 (5.14–7.53)	<0.001
FPI, mIU/L	8.91 (5.97–13.15)	8.85 (6.16–12.41)	0.511
HOMA-IR	2.37 (1.58–3.89)	2.19 (1.48–3.20)	0.020
TG, mmol/L	1.30 (0.91–1.91)	1.14 (0.82–1.68)	0.014
HDL-C, mmol/L	1.29 (1.10–1.56)	1.40 (1.20–1.65)	0.001
LDL-C, mmol/L	3.50 ± 0.86	3.27 ± 0.87	0.005
TC, mmol/L	5.32 ± 0.96	5.08 ± 0.95	0.007
BMI, kg/m <sup>2</sup>	26.03 ± 3.26	24.93 ± 3.11	<0.001
Smoking			0.002
Current smoker (n = 138)	71 (51.4%)	67 (48.6%)	
Noncurrent smoker (n = 336)	120 (35.7%)	216 (64.3%)	
Drinking			0.009
Current drinker (n = 199)	94 (47.2%)	105 (52.8%)	
Noncurrent drinker (n = 275)	97 (35.3%)	178 (64.7%)	
Hypertension			<0.001
With hypertension (n = 283)	136 (48.1%)	147 (51.9%)	
Without hypertension (n = 191)	55 (28.8%)	136 (71.2%)	
Obesity			0.076
With obesity (n = 93)	45 (48.4%)	48 (51.6%)	
Without obesity (n = 381)	146 (38.3%)	235 (61.7%)	
NAFLD			0.006
With NAFLD (n = 176)	85 (48.3%)	91 (51.7%)	
Without NAFLD (n = 298)	106 (35.6%)	192 (64.4%)	
Diabetes			<0.001
With diabetes (n = 108)	72 (66.7%)	36 (33.3%)	
Without diabetes (n = 366)	119 (32.5%)	247 (67.5%)	
IFG			0.842
With IFG (n = 12)	4 (33.3%)	8 (66.7%)	
Without IFG (n = 462)	187 (40.5%)	275 (59.5%)	
IGT			0.004
With IGT (n = 70)	39 (55.7%)	31 (44.3%)	
Without IGT (n = 404)	152 (37.6%)	252 (62.4%)	

BMI = body mass index, DBP = diastolic blood pressure, FPG = fasting plasma glucose, FPI = fasting plasma insulin, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, IFG = impaired fasting glycaemia, IGT: impaired glucose tolerance, LDL-C = low-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride.

IFG, and obesity populations was similar to that in non-IFG, and nonobesity populations, respectively.

### Prevalence of Carotid Atherosclerosis at Different Age Intervals

As shown in Table 1, age and gender were strongly correlated with CA. Based on the age distribution (40–70 years), the participants were divided into three age groups in 10-year increments in order to calculate the prevalence of CA in different age groups. In addition, the participants were also divided into male and female groups to separately assess differences in the

prevalence of CA in each age group. As shown in Table 2, the prevalence of CA in the whole study population increased with age. In male and female subgroups, the prevalence of CA also increased with age for the 40 to 49-, 50 to 59-, and 60 to 70-year age groups. CA was more frequent in male participants than in female participants in all age groups (24.2% vs. 11.9%, 57.0% vs. 23.5%, and 80.0% vs. 54.4%, respectively).

### Potential Risk Factors of Carotid Atherosclerosis

The prevalence of CA in the presence of different factors was analyzed separately for men and women; the results are

**TABLE 2.** Prevalence of Carotid Atherosclerosis in the Three Different Age Intervals

Variable	40–49	50–59	60–70
Male			
Total number	62	114	55
Carotid atherosclerosis	15 (24.2%)	65 (57.0%)	44 (80.0%)
Female			
Total number	67	119	57
Carotid atherosclerosis	8 (11.9%)	28 (23.5%)	31 (54.4%)
Both male and female			
Total number	129	233	112
Carotid atherosclerosis	23 (17.8%)	93 (39.9%)	75 (67.0%)

shown in Table 3. The prevalence of CA was significantly higher in diabetics than in nondiabetics (men: 71.4% vs. 46.0%, women: 57.9% vs. 22.0%; all *P*-values < 0.05). Because the overall prevalence of CA increased with age, as well as in both

men and women respectively (Table 2), the participants were divided into over-60-year-old and below-60-year-old groups. The prevalence of CA was significantly higher in the over-60-year-old group than in the below-60-year-old group (men: 80.0% vs. 45.5%, women: 54.4% vs. 19.4%, all *P*-values < 0.05). Among male participants, the prevalence of CA was significantly higher in the high TC and high LDL-C populations than in the control group consisting of individuals with blood biochemical analysis results within normal ranges. It should be noticed that all these results only apply to male participants (all *P*-values < 0.05). In female participants, the prevalence of CA was significantly higher in high TG, hypertensive, obese and NAFLD groups than in the control group (all *P*-values < 0.05). However, HDL-C level, smoking, and alcohol consumption did not significantly influence the prevalence of CA in men or women.

### Logistic Regression Analysis of Risk Factors

Logistic regression analysis was performed in order to investigate factors that independently affected the prevalence of CA. Age, gender, and diabetes significantly affected the

**TABLE 3.** Prevalence of Carotid Atherosclerosis in the Male and Female Participants Based on Several Potential Risk Factors

Variable	Men (n = 231)				Women (n = 243)			
	N	n (%)	OR (95% CI)	<i>P</i>	N	n (%)	OR (95% CI)	<i>P</i>
Age, years								
≥60	55	44 (80.0%)	4.80 (2.33–9.90)	<0.001	57	31 (54.4%)	4.97 (2.63–9.38)	<0.001
<60	176	80 (45.5%)	Ref		186	36 (19.4%)	Ref	
TC, mmol/L								
≥5.18	100	64 (64.0%)	2.10 (1.23–3.59)	0.006	124	40 (32.3%)	1.62 (0.92–2.87)	0.095
<5.18	131	60 (45.8%)	Ref		119	27 (22.7%)	Ref	
TG, mmol/L								
≥1.7	80	41 (51.3%)	0.86 (0.50–1.48)	0.590	49	20 (40.8%)	2.16 (1.12–4.16)	0.020
<1.7	151	83 (55.0%)	Ref		194	47 (24.2%)	Ref	
HDL-C, mmol/L								
<1.04	52	24 (46.2%)	0.68 (0.36–1.26)	0.216	12	5 (41.7%)	1.95 (0.60–6.36)	0.430
≥1.04	179	100 (55.9%)	Ref		231	62 (26.8%)	Ref	
LDL-C, mmol/L								
≥3.37	104	67 (64.4%)	2.22 (1.31–3.79)	0.003	124	40 (32.3%)	1.62 (0.92–2.87)	0.095
<3.37	127	57 (44.9%)	Ref		119	27 (22.7%)	Ref	
Hypertension								
Yes	167	93 (55.7%)	1.34 (0.75–2.38)	0.323	116	43 (37.1%)	2.53 (1.41–4.53)	0.002
No	64	31 (48.4%)	Ref		127	24 (18.9%)	Ref	
Current smoker								
Yes	125	68 (54.4%)	1.07 (0.63–1.79)	0.812	13	3 (23.1%)	0.78 (0.21–2.92)	0.957
No	106	56 (52.8%)	Ref		230	64 (27.8%)	Ref	
Current drinker								
Yes	170	89 (52.4%)	0.82 (0.45–1.47)	0.500	29	5 (17.2%)	0.51 (0.19–1.40)	0.185
No	61	35 (57.4%)	Ref		214	62 (29.0%)	Ref	
Obesity								
Yes	55	28 (50.9%)	0.86 (0.47–1.58)	0.637	38	17 (44.7%)	2.51 (1.23–5.13)	0.010
No	176	96 (54.5%)	Ref		205	50 (24.4%)	Ref	
NAFLD								
Yes	95	54 (56.8%)	1.24 (0.73–2.10)	0.420	81	31 (38.3%)	2.17 (1.21–3.88)	0.008
No	136	70 (51.5%)	Ref		162	36 (22.2%)	Ref	
Diabetes								
Yes	70	50 (71.4%)	2.94 (1.61–5.38)	<0.001	38	22 (57.9%)	4.89 (2.37–10.08)	<0.001
No	161	74 (46.0%)	Ref		205	45 (22.0%)	Ref	

HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NAFLD = nonalcoholic fatty liver disease, TC = total cholesterol, TG = triglyceride.

**TABLE 4.** Logistic regression analysis of risk factors of carotid atherosclerosis

Variable	$\beta$	OR	95% CI	P
Age (per 10 years)	1.135	3.11	2.21–4.39	<0.001
Gender (male/female)	1.318	3.74	1.99–7.03	<0.001
Diabetes (yes/no)	1.114	3.05	1.82–5.10	<0.001

CI = confidence interval, OR = odds ratio.

prevalence of CA (Table 4, all *P* values <0.05). The results of this analysis also indicated that the likelihood of CA prevalence increases with age, and that men, and patients with diabetes are more likely to have CA than women, and the nondiabetic population, respectively. The variables excluded by the logistic regression analysis included hypertension, obesity, smoking, alcohol consumption, high LDL-C, high TC, high TG, low HDL-C, NAFLD, IGT, and IFG.

## DISCUSSION

This epidemiological survey was conducted on a representative group of relatively healthy community residents. The primary objective of this study was to identify factors significantly associated with CA. Our results indicate that age, gender, and diabetes significantly affect the prevalence of CA. Other studies reported hypercholesterolemia,<sup>18</sup> obesity,<sup>19</sup> hypertension,<sup>20</sup> and other factors to be additional risk factors associated with CA. However, as shown in this study, these factors were only associated with the prevalence of CA in either men or women and showed no significant correlation with the prevalence of CA in the overall population. For example, high TC level was associated with CA in men, but showed no significant correlation with the prevalence of CA in women. Among women in this study, the prevalence of CA in obese, and hypertensive participants was higher than in their corresponding control groups, yet this trend was not observed in male participants. With the increasing prevalence of CA, the identification of factors that significantly affect the occurrence of CA will contribute to the development of preventive and therapeutic strategies.

Our study results show increasing prevalence of CA with age. These findings are consistent with the results of other studies; namely, that age is an independent risk factor of CA.<sup>21</sup> Our study detected a gradual increase in the CA prevalence with age, similar to the results of a previous study that reported increasing intima-media thickness (IMT) of carotid artery with age in young adults.<sup>22</sup> The mechanisms underlying the relation between CA and age can be explained as follows. The media of elastic arteries consist of several types of cells, however, smooth muscle cells are the major cellular constituents, which can begin to degenerate through apoptosis in middle-aged individuals, resulting in the reduction of elastic fibers by degenerating and thinning.<sup>23</sup> Because elastin has a very slow rate of turnover, it likely suffers from glycol-oxidative reaction,<sup>24</sup> and the accumulation of glycol-oxidative products in the aortic media increases with advancing age.<sup>25</sup>

The results of this study indicate that gender is closely correlated with the occurrence of CA. The reason for this difference might be differing levels of endogenous sex hormones between men and women. Estrogen has been reported to reduce the incidence of CA by lowering LDL-C level and

reducing intravascular inflammation.<sup>26</sup> Some studies have reported that levels of both TC and LDL-C can be reduced through estrogen therapy, which can also raise HDL-C primarily by interfering with expression of hepatic apoprotein genes at the same time.<sup>27</sup> Estrogen can also alleviate the inflammatory nature of atherosclerosis by influencing monocyte adherence to the intimal surface of endothelium as well as subendothelial migration.<sup>28</sup> Moreover, estrogen may also slow down the influx of net arterial cholesterol.<sup>29</sup>

The results of this study also show that diabetes is a risk factor for CA. In other studies, poor plasma glucose control and long diabetes course had significant adverse effects on IMT of carotid artery in young patients with type 2 diabetes, indicating that the development of useful methods to get better plasma glucose control in these patients is necessary to prevent and limit the occurrence and development of atherosclerotic cardiovascular disorders.<sup>30</sup> Moreover, another study reported significantly greater IMT of carotid artery even in prediabetic individuals with IGT compared to age- and gender-matched controls.<sup>31</sup> The pathogenesis underlying the associations between diabetes and CA can be explained as follows. Diabetes can damage endothelium-dependent vasodilation through reducing the bioavailability of endothelium-derived nitric oxide (NO),<sup>32</sup> which is a main antiatherosclerotic factor.<sup>33</sup> Hyperglycemia restrains production of NO through hindering the activation of endothelial NO synthase and promoting the production of reactive oxygen species,<sup>34</sup> which can directly decrease NO bioavailability.<sup>35</sup> As for platelets, studies have demonstrated that mean platelet volume is significantly related to the severity of diabetes,<sup>36</sup> and individuals with larger platelets have more prothrombotic potential than those with smaller platelets.<sup>37,38</sup> Moreover, diabetics are often insulin insufficient and/or demonstrate insulin resistance, and insulin is a natural antagonist of platelet hyperactivity, which can promote endothelial production of prostacyclin (PGI<sub>2</sub>) and sensitize the platelets to PGI<sub>2</sub>. Therefore, the defects in insulin action lead to abnormal platelet activity, which can eventually result in that the adhesion of platelet to vascular endothelium in diabetics is readier than that in healthy individuals.<sup>39</sup>

The prevalence of hypertension, obesity, NAFLD, and diabetes in this study population was 59.7% (283/474), 19.6% (93/474), 37.1% (176/474), and 22.8% (108/474), respectively (as shown in Table 1). The previously reported prevalence of hypertension, obesity, NAFLD, and diabetes in Chinese populations are 59.4% to 65.2%,<sup>40,41</sup> 12.4%,<sup>42</sup> 42%,<sup>43</sup> and 11.6%,<sup>44</sup> respectively. Thus, the hypertension and NAFLD results in our survey are consistent with previous reports, but the prevalence of obesity and diabetes in our survey is higher. The rate of obesity in the Chinese population was reported to be lower in South China and higher in North China, particularly in Northeast China, which has the highest obesity prevalence in China. The first reason for this phenomenon is that the higher latitude means colder weather. Hot weather can promote the metabolism of human, which could be reflected in the lower prevalence of obesity in South China compared to North China and especially Northeast China, in which the winter is significantly colder. The second reason for this phenomenon is that of eating habits. The people in Northeast China typically consume a higher cholesterol diet and more likely to drink than people in South China, which consistent with having a higher prevalence of obesity than the general Chinese population. In the case of diabetes, in addition to the aforementioned factors affecting obesity, a third reason is that the population surveyed in that previous report had a minimum age of 18 years, and thus

included many young people. However, the population in our study was between 40 and 70 years of age. As the occurrence of diabetes increases with age, we think the prevalence of diabetes in our study is acceptable.

Although all reasonable precautions have been taken regarding the epidemiological survey and statistical analysis, this paper has several limitations. First, the data used for statistical analysis were from the cross-sectional study, thus they can only be used to reflect the factors correlated with the prevalence of CA at a single time point, and not to predict disease development and prognosis. Second, this study used ultrasonography examinations to diagnose CA and NAFLD, which is less accurate than pathological diagnosis obtained from biopsy specimens. However, biopsy is invasive, expensive, and time- and energy-consuming, which limit its application in large-scale epidemiological studies. Ultrasonography is non-invasive, less expensive, and repeatable, so it is considered a relatively reliable examination method applicable to clinical practices and epidemiological studies.<sup>45</sup> Third, all residents participating in this epidemiological survey were from Northeast China, which limits the generalizability of the study results to other ethnic groups, who may have different genetic backgrounds, lifestyles, and sociodemographic characteristics. Hence, more studies, especially in other ethnic groups, are needed to verify our study findings, and the results of this study should be interpreted with discretion.

In conclusion, we found that older age, male sex, and diabetes individually increase the risk of CA in Northeast Chinese population. These findings could lead to improved screening for CA for better disease management.

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