



Research Paper

High milk consumption is associated with carotid atherosclerosis in middle and old-aged Chinese

Miao He^a, Zaogeng Guo^b, Zuxun Lu^d, Sheng Wei^a, Zhihong Wang^{b,c,*}^a Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China^b Health Science Center, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen, China^c Guangdong Innovation Platform for Translational Research for Cerebrovascular Diseases, Shenzhen, China^d Department of Social Medicine and Health Management, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

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ABSTRACT

Background: Carotid atherosclerosis (CA) can reflect atherosclerotic status of systemic vessels, and is associated with ischemic stroke and cognitive impairment. Milk consumption is growing in China, and data are limited on the association between milk and CA risk.

Methods: Participants aged ≥ 40 years in China National Stroke Prevention Project were recruited for carotid ultrasound examination, and those with carotid endarterectomy, carotid stenting stroke or coronary heart disease were excluded. Participants were defined as having CA when intima-media thickness (IMT) ≥ 1 mm or plaques were detected by ultrasonography. For milk consumption, though contents were not analyzed, people were divided into high consumption (≥ 200 ml/day and ≥ 5 day/week) and low consumption (occasional or never) groups. Multivariate logistics regression analyses were done in both full and propensity score-matched population to identify the association between milk consumption and CA.

Results: 84880 participants were included in the final analysis. After being adjusted by age, gender, living location, smoking habits, drinking habits, physical activity, obesity, hypertension, diabetes, and dyslipidemia, high milk consumption is associated with CA in both full population (odds ratio [OR] = 1.26, 95% confidence interval [CI] 1.19–1.33) and propensity score-matched population (OR = 1.25, 95%CI 1.17–1.34). High milk consumption is also a risk factor for IMT thickening (OR = 1.15, 95%CI 1.08–1.23), carotid plaque formation (OR = 1.17, 95%CI 1.09–1.25) and carotid stenosis over 50% (OR = 1.52, 95%CI 1.10–2.14) in the propensity score-matched population.

Conclusions: High milk consumption is related to CA in middle and old-aged Chinese population. More cautious advice on milk intake should be given in this population for prevention of atherosclerosis.

1. Introduction

Atherosclerosis is a systemic vascular condition, which can be recognized in large and medium-sized arteries [1,2]. Carotid atherosclerosis, which is a commonly detected form of atherosclerosis, can lead to ischemic stroke and cognitive impairment [3,4]. Studies have found that atherosclerotic process may start at a young age and proceed for many years before the onset of symptoms [5,6]. Thus, controlling the development of carotid atherosclerosis may reduce the burden of related diseases. Many lifestyle factors, especially the dietary factors, have been reported to contribute to the development of atherosclerosis [7,8]. Among them, the effect of dairy products on cardiovascular disease (CVD) risk has been studied in diverse populations [9]. Several recent

systematic reviews suggested that there were no associations between dairy consumption and risk of CVD [10,11], but other meta-analysis found an inverse relationship between high dairy intake and risk of CVD in women [12]. Thus, the roles of milk consumption in the development of CVD, including the pathogenesis of atherosclerosis, are still discordant.

Being a key source of protein from diet, milk also contains diverse kinds of lipids, carbohydrates, vitamins, and minerals. The lipids in milk have been thought to be atherogenic and contribute to the risk of CVD in developed countries [13]. But some studies argued that the effect of milk-derived lipids on CVD progression depends on the distinct functions of saturated and unsaturated fatty acids [14,15]. Other components in milk can also play divergent roles in the process of atherosclerosis [16].

* Corresponding author. Health Science Center, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen, China.

E-mail address: wangzhihongsz@yeah.net (Z. Wang).

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The high variability in the composition and amount of nutritional components in milk contributes to the complexity of the effect on cardiometabolic function [17]. Such complexity of biological mechanisms may be the underlying cause of the inconsistent findings from epidemiology studies.

With the rapid economic development in China, the daily intake of dairy products is increasing quickly. Although dairy has long been the an essential part of diet in developed countries, it has just begun to be popular in China during the recent decades [18]. Unlike the dairy consumption patterns in developed countries, milk rather than cheese is the main consumed dairy product in Chinese population. Recent meta-analyses suggested that dairy product consumption is not associated with cardiovascular mortality, but the studies included in the analyses focused on the cheese consumption [19,20]. Thus, studies are needed to verify the exact role of milk consumption in Chinese population. Since most of the milk consumed by Chinese population was whole-fat milk [21,22], results might also reflect hazards related to the fat content of the milk, those the contents of milk were not analyzed in this study.

1.1. Aims and hypothesis

In this study, we aimed to explore the associations between milk consumption and the probabilities of carotid atherosclerosis and carotid atherosclerosis-related ultrasound findings, including carotid intima-media thickening, carotid plaque formation, and carotid stenosis, in a nationally representative Chinese population with ages being ≥ 40 years old. We hypothesize that milk consumption may be associated with risks of carotid atherosclerosis in middle and old-aged Chinese adults.

2. Methods

2.1. Study subjects and design

This study used the data from China National Stroke Screening and Prevention Project (CNSSPP), a large national stroke screening survey which was carried out from October 2014 to November 2015. The design of CNSSPP has been well described previously [23]. In brief, 200 project areas from 31 provinces (without Tibet) in China were selected by a 2-staged stratified cluster sampling method. Afterward, one urban community and one rural village were chosen from each project area as primary sampling units, in accordance with the geographical locations and suggestions of local hospitals. All residents with ages being ≥ 40 years were surveyed during the primary screening.

2.2. Carotid ultrasound measurement

Qualified ultrasound physicians performed carotid ultrasonography examinations, and Chinese stroke vascular ultrasound examination guidelines were strictly followed while conducting all examining procedures. All participants were examined in the supine position. Ultrasound systems, including Logiq 9 (GE Healthcare), iU22 (Philips Healthcare), S2000 (Siemens Medical Solutions), with the probe transmission frequency of 6–10 MHz, were employed in the examinations. Atherosclerotic plaques were screened in each common carotid artery, internal carotid artery, external carotid artery, and bulb in the longitudinal and transverse planes. Intima-media thickness (IMT) was measured manually 3 times for every participant on a plaque-free area that was 1.0–1.5 cm away from the carotid bifurcation, and the averaged thickness from the three measurements was recorded as intima-media thickness.

Participants were diagnosed with carotid atherosclerosis (CA) when increased IMT or plaques were screened out by ultrasonography. Increased IMT was defined as $\text{IMT} \geq 1$ mm in either the left or the right carotid artery. Participants were considered as having plaques when $\text{IMT} \geq 1.5$ mm or focal narrowing of the vessel wall $>50\%$ in relation to

adjacent segments were found in ultrasound examination. Stenosis severity was classified as normal (no stenosis), $<50\%$, 50% – 69% , 70% – 99% , and occlusion. Moderate stenosis was recorded when 50% – 69% narrowing was detected, and severe stenosis was recorded when $\geq 70\%$ stenosis was detected. For those with bilateral carotid artery measurements, the more severe classification was used for evaluation. A total of 726, 451 participants were included in CNSSPP, and 107, 095 of them underwent the carotid examination. As people with carotid endarterectomy or carotid stenting and those with a history of stroke or coronary heart disease may have undergone interventions, which are difficult to be adjusted for in analysis of covariates, they were excluded from subsequent analysis. Finally, the total population in this study included 84, 880 participants (45, 515 women and 39, 365 men).

2.3. Milk consumption and covariates

According to the items in the survey questionnaire, milk consumption was classified as high consumption (≥ 200 ml/day and ≥ 5 day/week) or low consumption (occasional or never) [24,25]. Due to the design of this study, contents of the milk consumed were not measured. All covariates, including age, gender, smoking status, alcohol consumption, physical activity, and medication were self-reported. Smoking status was divided into current, past, or never smoking. Alcohol consumption was classified as regular drinking (≥ 3 times/week), occasional drinking (< 3 times/week), or never drinking. Physical activity was defined as regular exercise if one does exercise for over 3 times/week and at least 30 min per session.

Body weight, height and blood pressures were measured in the physical examination. Body mass index (BMI) was defined as body weight (in kg) divided by the square of height (in m). Obesity was defined as $\text{BMI} \geq 28$, according to the guidelines of the working Group on Obesity in China. Blood pressure (BP) was calculated using the average of 3 measurements with 1-min intervals after 5 min of rest. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported hypertension diagnosed by a qualified physician, or history of antihypertensive medications. Blood samples were collected to test fasting plasma glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Diabetes mellitus was defined as fasting plasma glucose ≥ 7.0 mmol/L, self-reported diagnosis of diabetes mellitus by a qualified physician, or use of oral hypoglycemic agents or insulin injection. Dyslipidemia was defined as having one or more of the following abnormal results in serum lipid tests: triglyceride ≥ 2.26 mmol/L, total cholesterol ≥ 6.22 mmol/L, high-density lipoprotein cholesterol < 1.04 mmol/L, low-density lipoprotein cholesterol ≥ 4.14 mmol/L, self-reported diagnosis of dyslipidemia by a qualified physician, or taking cholesterol-lowering medications.

2.4. Statistical analysis

Descriptive statistics were performed for both the full and the propensity score-matched population. Continuous variables were described by mean \pm standard deviation and categorical variables were presented as percentages. We employed *t* tests for comparison between two continuous variables, and χ^2 tests for comparing the proportion of categorical variables. The association between milk consumption and carotid ultrasonography results was assessed by multivariate logistic regression analysis with adjusting for confounding covariates, including age, gender, living location, obesity, smoking, alcohol consumption, physical activity, hypertension, diabetes mellitus, and dyslipidemia. To control for the potential selection bias, propensity score-matched analysis was performed. We estimated the propensity score for each patient with high or low milk consumption using a multivariate logistic regression model. The following variables were included in the model: age, gender (male or female), location (urban or rural), smoking (current, past, or never), drinking (regular, occasional, or never), physical activity

Table 1
Characteristics of the study population.

	Total population				Propensity score-matched population			
	Total (n = 84880)	Low milk consumption (n = 77222)	High milk consumption (n = 7658)	P	Total (n = 15242)	Low milk consumption (n = 7621)	High milk consumption (n = 7621)	P
Age (years)	60.68 ± 10.30	60.53 ± 10.29	62.21 ± 10.34	<.001	62.16 ± 10.22	62.11 ± 10.08	62.22 ± 10.36	0.507
Gender, n (%)								
Male	39365 (46.38)	36276 (46.98)	3089 (40.34)	<.001	6117 (40.13)	3040 (39.89)	3077 (40.38)	0.541
Female	45515 (53.62)	40946 (53.02)	4569 (59.66)		9125 (59.87)	4581 (60.11)	4544 (59.62)	
Location, n (%)								
Urban	40660 (47.90)	34980 (45.30)	5680 (74.17)	<.001	11291 (74.08)	5647 (74.10)	5644 (74.06)	0.956
Rural	44220 (52.10)	42242 (54.70)	1978 (25.83)		3951 (25.92)	1974 (25.90)	1977 (25.94)	
Smoking, n (%)								
Never smoking	59653 (70.28)	53997 (69.92)	5656 (73.86)	<.001	11313 (74.22)	5685 (74.60)	5628 (73.85)	0.571
Past smoking	3873 (4.56)	3378 (4.37)	495 (6.46)		970 (6.36)	477 (6.26)	493 (6.47)	
Current smoking	21354 (25.16)	19847 (25.70)	1507 (19.68)		2959 (19.41)	1459 (19.14)	1500 (19.68)	
Drinking, n (%)								
Never drinking	69802 (82.24)	63596 (82.35)	6206 (81.04)	<.001	12358 (81.08)	6183 (81.13)	6175 (81.03)	0.970
Occasional drinking	9460 (11.15)	8501 (11.01)	959 (12.52)		1902 (12.48)	946 (12.41)	956 (12.54)	
Regular heavy drinking	5618 (6.62)	5125 (6.64)	493 (6.44)		982 (6.44)	492 (6.46)	490 (6.43)	
Physical activity								
Regular physical activity	41733 (49.17)	38114 (49.36)	3619 (47.26)	<.001	7251 (47.57)	3661 (48.04)	3590 (47.11)	0.250
Lack of physical activity	43147 (50.83)	39108 (50.64)	4039 (52.74)		7991 (52.43)	3960 (51.96)	4031 (52.89)	
BMI, (kg/m ²)	25.70 ± 3.70	25.72 ± 3.72	25.52 ± 3.46	<.001	25.55 ± 3.52	25.58 ± 3.58	25.52 ± 3.46	0.293
Systolic BP (mmHg)	138.56 ± 21.69	138.74 ± 21.78	136.67 ± 20.63	<.001	137.14 ± 20.52	137.28 ± 21.42	137.00 ± 19.57	0.408
Diastolic BP (mmHg)	84.43 ± 13.09	84.62 ± 13.13	82.50 ± 12.45	<.001	82.74 ± 12.36	82.77 ± 12.88	82.71 ± 11.81	0.721
Fasting plasma glucose (mmol/L)	6.09 ± 2.01	6.07 ± 2.00	6.26 ± 2.11	<.001	6.25 ± 2.09	6.24 ± 2.07	6.26 ± 2.11	0.480
Serum triglycerides (mmol/L)	1.91 ± 1.47	1.92 ± 1.48	1.80 ± 1.32	<.001	1.80 ± 1.24	1.79 ± 1.15	1.80 ± 1.32	0.467
Serum total cholesterol (mmol/L)	5.04 ± 1.16	5.04 ± 1.16	5.01 ± 1.15	0.019	5.01 ± 1.14	5.01 ± 1.13	5.01 ± 1.15	0.904
Serum LDL cholesterol (mmol/L)	2.91 ± 0.97	2.91 ± 0.97	2.90 ± 0.95	0.408	2.92 ± 0.96	2.89 ± 0.98	2.90 ± 0.95	0.695
Serum HDL cholesterol (mmol/L)	1.43 ± 0.56	1.43 ± 0.57	1.40 ± 0.48	<.001	1.40 ± 0.50	1.40 ± 0.52	1.40 ± 0.48	0.813
Obesity, n (%)	19690 (23.20)	18070 (23.40)	1620 (21.15)	<.001	3245 (21.29)	1636 (21.47)	1609 (21.11)	0.593
History of hypertension, n (%)	55663 (65.58)	50556 (65.47)	5107 (66.69)	0.032	10199 (66.91)	5115 (67.12)	5084 (66.71)	0.594
History of diabetes, n (%)	20235 (23.84)	17811 (23.06)	2424 (31.65)	<.001	4760 (31.23)	2347 (30.80)	2413 (31.66)	0.249
History of dyslipidemia, n (%)	37011 (43.60)	32771 (42.44)	4240 (55.37)	<.001	8093 (53.10)	3871 (50.79)	4222 (55.40)	<.001
Hypertension, n (%)	64101 (75.52)	58293 (75.49)	5808 (75.84)	0.491	11597 (76.09)	5813 (76.28)	5784 (75.90)	0.581
Diabetes, n (%)	24904 (29.34)	22085 (28.60)	2819 (36.81)	<0.001	5613 (36.83)	2806 (36.82)	2807 (36.83)	0.987
Dyslipidemia, n (%)	53510 (63.04)	48120 (62.31)	5390 (70.38)	<0.001	10644 (69.83)	5291 (69.43)	5353 (70.24)	0.274
Carotid atherosclerosis, n (%)				<0.001				<.001
No	42916 (50.56)	39655 (51.35)	3261 (42.58)		6877 (45.12)	3627 (47.59)	3250 (42.65)	
Yes	41964 (49.44)	37567 (48.65)	4397 (57.42)		8365 (54.88)	3994 (52.41)	4371 (57.35)	
Carotid intima-media thickening, n (%)				<0.001				<.001
No	54918 (64.70)	50376 (65.24)	4542 (59.31)		9294 (60.98)	4767 (62.55)	4527 (59.40)	
Unilateral	6944 (8.18)	6235 (8.07)	709 (9.26)		1408 (9.24)	709 (9.30)	699 (9.17)	
Bilateral	23018 (27.12)	20611 (26.69)	2407 (31.43)		4540 (29.79)	2145 (28.15)	2395 (31.43)	
Carotid plaques, n (%)				<0.001				<.001
0	53077 (62.53)	48788 (63.18)	4289 (56.01)		8811 (57.81)	4537 (59.53)	4274 (56.08)	
1	15721 (18.52)	14277 (18.49)	1444 (18.86)		2943 (19.31)	1510 (19.81)	1433 (18.80)	
≥2	16082 (18.95)	14157 (18.33)	1925 (25.14)		3488 (22.88)	1574 (20.65)	1914 (25.11)	
Carotid stenosis				<0.001				0.088
No	76388 (90.00)	69677 (90.23)	6711 (87.63)		13416 (88.02)	6721 (88.19)	6695 (87.85)	
1%–49%	7772 (9.16)	6915 (8.95)	857 (11.19)		1677 (11.00)	841 (11.04)	836 (10.97)	
50%–69%	540 (0.64)	471 (0.61)	69 (0.90)		118 (0.77)	49 (0.64)	69 (0.91)	
70%-blocked	180 (0.21)	159 (0.21)	21 (0.27)		31 (0.20)	10 (0.13)	21 (0.27)	

(regular exercise or not), obesity (yes or not), hypertension (yes or not), diabetes (yes or not), dyslipidemia (yes or not). We performed 1:1 nearest-neighbor matching based on the propensity score. We confirmed the success of the propensity matching procedure by re-comparing the characteristics between high and low consumption group. All analyses were performed by SAS 9.4 (SAS Institute Inc.), and a 2-tailed $P < 0.05$ was considered statistically significant.

3. Results

The characteristics of the full and propensity score-matched population were shown in Table 1. During the study period, 107, 095 individuals underwent a carotid ultrasound examination. After excluding those participants with a history carotid endarterectomy, stenting, or a history of stroke or coronary heart disease, 84, 880 individuals were included in the final analysis. Of these, 77, 222 individuals had a low level of milk consumption, while 7, 658 individuals had a high level of milk consumption.

For the full population of 84, 880 participants, 46.4% were men, 52.1% lived in rural areas. The mean age was 60.7 ± 10.3 years. Age, gender, living location, cigarette smoking, drinking behavior, and physical activity level were significantly different between those with low and high consumption of milk. The distributions of BMI, BP, fasting plasma glucose, serum lipid levels also showed a significant difference between these two groups. For the propensity score-matched population, 7, 621 individuals from the group of high milk consumption and 7, 621 individuals from the group of low milk consumption were included in the 1:1 propensity score matching. In this way, the baseline characteristics were well balanced between these two groups.

Then we did the multivariate logistic regression for the association between milk consumption and carotid ultrasonography in the full and the propensity score-matched populations (shown in Table 2.). High milk consumption is associated with increased probabilities of carotid atherosclerosis, increased IMT, bilaterally increased carotid IMT, carotid plaque formation, multiple carotid plaque formation and carotid stenosis of $\geq 50\%$ after adjusting for covariates including age, gender, living

location, smoking, drinking, physical activity, obesity, hypertension, diabetes and dyslipidemia in both the full population (OR = 1.26, 95%CI 1.19–1.33; OR = 1.15, 95%CI 1.09–1.21; OR = 1.15, 95%CI 1.05–1.25; OR = 1.18, 95%CI 1.13–1.23; OR = 1.30, 95%CI 1.23–1.37; OR = 1.28, 95%CI 1.02–1.55), and the propensity score-matched population (OR = 1.25, 95%CI 1.17–1.34; OR = 1.15, 95%CI 1.08–1.23; OR = 1.18, 95%CI 1.10–1.27; OR = 1.17, 95%CI 1.09–1.25; OR = 1.32, 95%CI 1.22–1.43; OR = 1.52, 95%CI 1.10–2.14). Since most of the milk consumed by Chinese population was whole-fat [21,22], the results suggested that the fat content can promote the development of carotid atherosclerosis, although the content of milk was not analyzed in this study.

Subgroup analyses were conducted by stratification with gender, age, and living location in the propensity score-matched population (shown in Table 3.). While high milk consumption was significantly associated with carotid atherosclerosis, carotid plaque formation, and multiple plaque formation after being stratified by gender and living location, the results did not apply to some age groups. For increased IMT, our results showed that only people living in urban areas were affected by high milk consumption. For the outcome of carotid stenosis $\geq 50\%$, the relationship was found only in men, participants with ages ≥ 70 years old, and those living in urban areas.

4. Discussion

In the present study, we found that high milk consumption is significantly associated with high probabilities of CA, together with chances of increased IMT, carotid plaque formation, and carotid stenosis, after being adjusted with the known risk factors of atherosclerosis, in both the full population and the propensity score-matched population. The association between high milk consumption and CA remains positive after being stratified by gender, and living location, and tends to be more significant in people ≥ 50 years old.

With the increasing popularity of milk in China, the potential effect of milk consumption on cardiovascular diseases needs to be well evaluated in Chinese. Since atherosclerosis is the main cause of cardiovascular

Table 2

High milk consumption in relation to carotid atherosclerosis, carotid intima-media thickening, carotid plaques and carotid stenosis in the full and propensity score-matched population.

	Full population		Propensity score-matched population	
	OR (95% CI)	P	OR (95% CI)	P
Carotid atherosclerosis				
Model 1	1.37 (1.30–1.44)	<0.001	1.25 (1.17–1.33)	<0.001
Model 2	1.30 (1.24–1.37)	<0.001	1.25 (1.17–1.33)	<0.001
Model 3	1.26 (1.19–1.33)	<0.001	1.25 (1.17–1.34)	<0.001
Increased IMT				
Model 1	1.24 (1.18–1.31)	<0.001	1.15 (1.07–1.23)	<0.001
Model 2	1.18 (1.12–1.24)	<0.001	1.15 (1.08–1.23)	<0.001
Model 3	1.15 (1.09–1.21)	<0.001	1.15 (1.08–1.23)	<0.001
Bilaterally increased IMT				
Model 1	1.21 (1.15–1.28)	<0.001	1.18 (1.10–1.26)	<0.001
Model 2	1.16 (1.10–1.23)	<0.001	1.18 (1.10–1.27)	<0.001
Model 3	1.15 (1.06–1.25)	<0.001	1.18 (1.10–1.27)	<0.001
Carotid plaque formation				
Model 1	1.29 (1.22–1.35)	<0.001	1.17 (1.09–1.25)	<0.001
Model 2	1.24 (1.18–1.30)	<0.001	1.17 (1.09–1.25)	<0.001
Model 3	1.18 (1.13–1.23)	<0.001	1.17 (1.09–1.25)	<0.001
Multiple carotid plaques				
Model 1	1.44 (1.35–1.51)	<0.001	1.31 (1.21–1.42)	<0.001
Model 2	1.35 (1.28–1.43)	<0.001	1.31 (1.21–1.42)	<0.001
Model 3	1.30 (1.23–1.37)	<0.001	1.32 (1.22–1.43)	<0.001
Carotid stenosis >50%				
Model 1	1.37 (1.10–1.72)	0.005	1.52 (1.09–2.11)	0.014
Model 2	1.35 (1.08–1.70)	0.010	1.51 (1.09–2.10)	0.015
Model 3	1.28 (1.02–1.55)	0.031	1.52 (1.10–2.14)	0.013

Model 1: Adjusted by age, gender.

Model 2: Model 1 + location, smoking, drinking, physical activity.

Model 3: Model 2 + obesity, hypertension, diabetes, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, lipid-lowering medication.

Table 3

High milk consumption in relation to carotid atherosclerosis stratified by gender, age, living location in propensity score-matched population.

	Carotid atherosclerosis	Increased IMT	Bilaterally increased IMT	Carotid plaque formation	Multiple carotid plaques	Carotid stenosis $\geq 50\%$
Gender						
Male	1.24 (1.11–1.38)	1.15 (1.04–1.28)	1.17 (1.06–1.30)	1.16 (1.05–1.29)	1.30 (1.16–1.47)	1.60 (1.04–2.45)
Female	1.27 (1.16–1.38)	1.16 (1.06–1.27)	1.19 (1.08–1.31)	1.18 (1.08–1.28)	1.34 (1.20–1.48)	1.41 (0.86–2.37)
Age (years)						
40–49	1.05 (0.84–1.31)	0.96 (0.75–1.22)	0.93 (0.70–1.23)	1.03 (0.79–1.34)	1.76 (1.11–2.79)	NA
50–59	1.30 (1.15–1.46)	1.30 (1.14–1.47)	1.21 (1.03–1.40)	1.05 (0.92–1.20)	1.11 (0.93–1.30)	0.61 (0.24–1.57)
60–69	1.24 (1.11–1.38)	1.11 (0.98–1.24)	1.11 (1.00–1.24)	1.20 (1.08–1.32)	1.31 (1.16–1.48)	2.24 (0.78–2.08)
≥ 70	1.28 (1.12–1.47)	1.17 (1.03–1.33)	1.31 (1.14–1.49)	1.28 (1.12–1.46)	1.43 (1.25–1.64)	2.82 (1.64–4.86)
Location						
Urban	1.21 (1.11–1.30)	1.19 (1.11–1.28)	1.22 (1.14–1.31)	1.15 (1.05–1.24)	1.34 (1.22–1.47)	1.65 (1.13–2.43)
Rural	1.39 (1.24–1.56)	1.05 (0.92–1.20)	1.03 (0.89–1.19)	1.28 (1.12–1.47)	1.30 (1.11–1.51)	1.19 (0.60–2.29)

*Controlled for age, gender, living location, smoking, drinking, physical activity, obesity, hypertension, diabetes, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, lipid-lowering medication.

diseases, the association between high milk consumption and high level of atherosclerosis may reflect the possible mechanisms underlying the risk of milk consumption in cardiovascular disease. Apart from the amount of milk consumption, the types of milk products are also significantly different between China and developed countries. For example, although fat-free milk has already become popular in western countries, whole milk is still the major consumed kind in China [21,22]. The saturated fat content in milk has been considered to contribute to the risk of CVD and current dietary guidelines recommend fat-free or low-fat instead of full-fat dairy products [26,27]. But a recent systematic review investigated the associations between biomarkers of dairy fat intake and risk of cardiovascular disease, and drew a conclusion that the levels of these circulating dairy fat biomarkers were not associated with an increased risk of CVD [28]. We found the significant effect of milk consumption on different markers of carotid atherosclerosis after controlling with dyslipidemia. These findings imply that more mechanisms may be involved in this pathological process besides the impact of saturated fat in milk. Considering the vital role in atherosclerotic cardiovascular disease (ASCVD), toxic trimethylamine N-oxide (TMAO) was reported to be converted from Trimethylamine (TMA) in milk by gut bacterial TMA lyases in a recent research [29]. Furthermore, TMAO was reported to contribute to the high atherosclerotic burden in patients with CAD [30]. Recent studies also found that the mechanisms of diet on CVD risk could be affected by the contribution of gut microbiota [31]. Considering the difference of gut microbiota between Chinese and people living in developed countries, the milk consumption may play different roles in CVD development among them. Nonetheless, the possible pathogenic effect of milk consumption should be taken into consideration for the dietary guidelines of Chinese middle and old-aged people.

The limitation of this study is that it is a cross-sectional study. The association between milk consumption and the level of carotid atherosclerosis may be not a causal relationship. However, with the large nationwide representative sample, the result of this study can still be considered as a piece of strong evidence for the linkage between milk consumption and carotid atherosclerosis. Also, as the detailed amount of milk consumption for each participant was not recorded, dose-response relationship was not explored in this study. But according to previous studies in Chinese population [24,25], the classification we used can effectively distinguish those with high milk consumption. Moreover, it should be mentioned that the fat content of milk was not measured in this study. However, since most of the milk consumed by Chinese population was whole-fat milk [21,22], it is quite possible that the results might reflect hazards related to the fat content of the milk and that opposite effects might be observed in fat-free milk. More studies are needed to identify the association between milk consumption and level of carotid atherosclerosis in the future.

In the present study, our findings suggested that the high level of milk consumption is associated with a high probability of carotid atherosclerosis in Chinese middle and old-aged people. This is the first evidence for the atherogenic effect of milk intake in a large Chinese population and

may provide some suggestions for the dietary guidelines in Chinese middle and old-aged adults.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

Miao He: Investigation, Writing - original draft, Formal analysis. **Zaogeng Guo:** Data curation. **Zuxun Lu:** Validation. **Sheng Wei:** Methodology. **Zhihong Wang:** Project administration, Funding acquisition.

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