Transition from Metabolically Healthy to Unhealthy Associated with Risk of Carotid Artery Plaque in Chinese Adults

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Original investigation

Keywords: metabolically healthy, metabolic abnormality, carotid artery plaque, adults

Posted Date: October 15th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-91098/v1>

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Abstract

Background: Limited data focused the transition from metabolically healthy to metabolic abnormalities on future risk of developing carotid artery plaque (CAP). We aimed to evaluate the association between the shift of metabolic status and future risk of CAP in community-based Chinese adults.

Methods: Blood pressure, fasting blood glucose, glycated hemoglobin A1c, lipid profiles, and carotid artery B ultrasonography were annually assessed throughout the study. Metabolically healthy were defined as participants without history of metabolic diseases and cancer but with normal value of aforementioned parameters at baseline (2013). If any of these parameters became abnormal during follow up, it was considered as the transition.

Results: Included were 9,836 Chinese adults (4,085 males and 5,751 females) who were metabolically healthy at baseline aged 35.8 ± 9.0 years. The most two common types of metabolic abnormalities during five years of follow up was high blood pressure (cumulative proportion: 36.4%) and impaired glucose regulation (20.1%). We have identified 133 incident cases of CAP during follow up. Compared to those who remained metabolically healthy, the transition to high blood pressure, high total cholesterol, high low-density lipoprotein cholesterol, or dyslipidemia was associated with high risk of developing carotid artery plaque (Hazard ratios (HRs) ranged from 1.69 to 2.34; $p < 0.05$ for all). The transition to impaired glucose regulation, high total triglycerides, and low high-density lipoprotein cholesterol, was associated with high risk of carotid artery plaque only in participants with metabolically healthy overweight at baseline (HR ranged from 1.95 to 4.62; $p < 0.05$ for all).

Conclusions: The transition from baseline metabolically healthy to metabolic abnormalities, was associated with high risk of incident carotid artery plaque.

Background

Although the prevalence of atherosclerosis varies in different age and ethnic population (1, 2) and most of atherosclerosis are asymptomatic, however, the presence of atherosclerosis obviously contributes to many adverse events, such as ischemic stroke and myocardial infarction, and impairment of cognitive function (3–5). Further, one-third cardiovascular related deaths are resulted from atherosclerosis, thus making it the leading cause of mortality worldwide (6).

Metabolic abnormalities such as high blood pressure, impaired glucose regulation, and dyslipidemia are considered as three major contributing factors to atherosclerosis. Because overweight and obesity is considered as the source of metabolic abnormalities, implementation of early intervention in subjects with overweight and obesity is both necessary and indispensable. However, a specific obesity phenotype, named as “metabolically healthy obesity”, aroused the arguments. Regardless of study design, sample size, and assessment of atherosclerosis, some studies reported a similar risk of developing atherosclerosis for metabolically healthy obesity to those with metabolically healthy normal weight (7–11), while others found that metabolically healthy obesity was also associated with a high risk of

developing atherosclerosis, relative to their normal-weight counterpart (12–20). The deficiency of standard definition of metabolically healthy obesity could partially explained the discrepancies among studies (21), however, the effects of the transition from baseline status of metabolically healthy obesity to metabolic abnormalities were neglected among previous studies. The longer duration of follow up could see the higher percent of transition (22). Data regarding the effects of the transition on the development of atherosclerosis is limited. To the best of our knowledge, only one cohort study to date evaluated the association of transition from metabolically healthy to unhealthy with the development of atherosclerosis (23). The transition, but not baseline metabolically healthy status, was associated with high risk of atherosclerosis (23). However, it has been doubtful to classify individuals with one metabolic risk factors, such as high blood pressure or impaired glucose regulation, as metabolically healthy status. Further, different metabolic abnormalities might exert different effects on the developing atherosclerosis, thus it is appropriate to evaluate these risk factors (such as high blood pressure, impaired glucose regulation) separately rather than combining them together (24).

Therefore, we performed the current study in community-based Chinese population with metabolically healthy status (absence of history of hypertension, diabetes mellitus, cardiovascular disease, dyslipidemia, and cancer and with normal blood pressure, blood glucose, lipid profile at baseline) and followed them for five years. Atherosclerosis is an umbrella term for a range of vascular conditions including coronary and carotid artery. The presence of carotid artery plaque is also associated with coronary artery plaque, thus might serve as an indicator for systematic atherosclerosis (25). We hypothesized that the onset of metabolic abnormalities was associated with future risk of carotid artery plaque (CAP), which was assessed by ultrasound B model annually.

Methods

Study population

All the participants were recruited from the Health Management Center in a teaching hospital from January 1, 2013 to December 31, 2018. All adult (≥ 18 years old) individuals receiving routine health checkup at our health management center were eligible for the study. An initial recruitment resulted in an identification of 109,410 subjects. Metabolically healthy were defined as participants without history of metabolic diseases but with normal blood pressure, fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c) level, and lipid profile at baseline (26). To recruit participants with metabolically healthy, we performed a sequential recruitment as following. First, we excluded participants with history of a series of metabolic diseases and cancer ($n = 9,651$), and those with baseline metabolic abnormalities [high blood pressure ($n = 37,134$), impaired glucose regulation ($n = 14,133$), and dyslipidemia ($n = 14,363$)]. Then, we excluded participants who lost to follow up ($n = 13,378$) and with missing data ($n = 8,083$). Finally, we excluded participants with low baseline BMI (≤ 18.4 kg/m², $n = 2,674$) (24), aged participants (≥ 65 years, $n = 79$), with CAP at baseline ($n = 78$), and with declined estimated glomerular filtration (eGFR < 60 ml/min/1.73 m², $n = 1$). Included were 9,836 (4,085 males and 5,751 females) Chinese adults with

mean age of 35.8 ± 9.0 years (Figure e-1). Participants included in the study tended to be younger, have higher proportion of women and lower baseline BMI, level of HbA1c, FBG, and blood pressure, compared with those who were out of the study (**Table e-1**). The study protocol was approved by the Ethical Committee of Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University. As a de-identified secondary data analysis, patients' consent was waived.

Blood pressure (systolic blood pressure and diastolic blood pressure), FBG, HbA1c, lipid profile [total cholesterol (TC), total triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)], and carotid artery B ultrasonography were annually assessed throughout the study (2013–2018).

Body weight (to the nearest 0.5 kg) and height (to the nearest 0.5 cm) was measured in standing position without shoes and in light clothing, using an electronic scale (SK-CK, Shuang Jia Company, Shanghai, China). BMI was calculated by body weight (kg) divided by height square (m^2). Blood pressure was measured twice using an automatic blood-pressure meter (HBP-9020, OMRON (China) Co., Ltd.) after participants were seated for at least 10 min. The average of two measurements was recorded for further analysis.

Venous blood samples were drawn and transfused into vacuum tubes containing EDTA in the morning after participants were fasted for at least six hours. An automatic analyzer (Roche 701 Bioanalyzer, Roche, UK) was used to measure FBG with the hexokinase/glucose-6-phosphate dehydrogenase method. The level of HbA1c was measured by high performance liquid chromatography, using the fully automated VARIANT™ II Hemoglobin Testing System (Bio-Rad, U.S). TC, TG, LDL-C, and HDL-C were measured by an automatic biochemical analyzer (Roche 701 Bioanalyzer, Roche, UK). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2-level race Eq. (27). The concentration of high sensitivity CRP (hs-CRP) was measured by immune-turbidimetric method. All the measurements were completed in the Clinical Laboratory of our hospital.

The history of hypertension, diabetes/impaired glucose regulation, dyslipidemia, cardiovascular diseases (stroke, hemorrhage, coronary artery bypass grafting, stent surgery, and ischemic infarction), was collected via a self-report questionnaire.

The transition from metabolically healthy status to metabolic abnormality (exposure)

The transition was deemed if any of the following abnormalities was confirmed during five-year follow up: high blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg) (28); impaired glucose regulation (FBG ≥ 5.6 mmol/L or HbA1c $\geq 5.7\%$) (29); high TC (TC ≥ 5.72 mmol/L); high TG (TG ≥ 1.7 mmol/L); high LDL-C (LDL-C ≥ 3.4 mmol/L); low HDL-C (HDL-C < 0.9 mmol/L in men and < 1.0 mmol/L in women). Dyslipidemia was defined as any of the four lipid parameters (TC, TG, LDL-C, and HDL-C) was confirmed abnormal based on above-mentioned references. In the secondary analysis, we evaluated the associated between baseline body weight status (metabolically healthy normal weight **vs.** metabolically healthy overweight) and the risk of transition to metabolic abnormalities. Participants

were classified into normal weight ($18.5 \leq \text{BMI} < 24.0 \text{ kg/m}^2$) or overweight ($\text{BMI} \geq 24.0 \text{ kg/m}^2$) groups based on the criteria for Chinese adults (30).

Assessment Of Cap (outcome)

Ultrasound B-mode imaging was performed annually to detect CAP during five-year follow-up (Philips HDI 5000 ultrasound system equipped with a 7.5 MHz probe). Intima-media thickness was measured at the point approximately 1.5 cm away from the distal part of the bifurcation of common carotid artery. CAP is defined as a focal region with a thickness $> 1.5 \text{ mm}$ as measured from the media adventitia interface to the lumen-intima interface or as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall (31).

Statistical analysis

Data were presented as mean $\pm$ standard deviation if it was in normal distribution and median and quartile range if it was in abnormal distribution. We completed all statistical analyses by SAS version 9.4 (SAS Institute, Inc, Cary, NC). Formal hypothesis testing will be two-sided with a significant level of 0.05. Because the conversion was confirmed at least twice, we determined the person-time of follow-up for each participant from January 1, 2014 to either the first onset date of the conversion, or the end of follow-up (December 31, 2018), whichever came first.

We used the proportional Cox regression model to evaluate the association between the transition and future risk of CAP. We adjusted the potential confounders in different models: model 1, adjusting for age (y) and sex; and model 2, further adjusting for baseline systolic blood pressure (mmHg), diastolic blood pressure (mmHg), FBG (mmol/L), HbA1c (%), TC (mmol/L), TG (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), eGFR (ml/min/1.73 m²) and hs-CRP (mg/L).

Likelihood ratio tests were conducted to examine statistical interactions between the transition and sex, and age, in relation to the CAP by comparing $-2 \log$ likelihood χ^2 between nested models with and without the cross-product terms.

To test the robustness of the main results, we conducted two sensitivity analyses in model 2. First, we censored participants whose baseline level of hs-CRP was 10.0 mg/L or more (32). Then, we censored participants who was confirmed with metabolic abnormalities once to lower the possibility of misclassification (26).

Results

The current study included 9,836 Chinese adults (4,085 males and 5,751 females) with metabolically healthy at baseline, with a mean age of 35.8 ± 9.0 years old. Metabolically healthy normal weight and overweight accounted for 76.4% ($n = 7,512$) and 23.6% ($n = 2,324$), respectively. Baseline characteristics

were significantly different between metabolically healthy normal weight and overweight groups except for total cholesterol (Table 1).

Table 1

Baseline characteristics in 9,836 Chinese adults who were metabolically healthy, according to baseline body weight status

Variables	Metabolically healthy normal weight	Metabolically healthy overweight	P value
Sample number	7,512	2,324	–
Age, y	35.6±8.9	36.3±9.3	< 0.001
Sex, M/F, %	34.9/65.1	63.1/36.9	< 0.001
BMI, kg/m ²	21.3±1.5	25.8±1.7	< 0.001
FBG, mmol/L	4.8±0.4	4.8±0.4	< 0.001
HbA1c, %	5.1±0.3	5.2±0.3	< 0.001
SBP, mmHg	108.2±9.7	112.8±8.7	< 0.001
DBP, mmHg	67.1±6.9	69.6±6.3	< 0.001
TC, mmol/L	4.4±0.6	4.4±0.6	0.08
TG, mmol/L	0.8±0.3	1.0±0.3	< 0.001
HDL-C, mmol/L	1.5±0.3	1.3±0.3	< 0.001
LDL-C, mmol/L	2.4±0.5	2.6±0.5	< 0.001
Hs-CRP, mg/L*	0.36 (0.2, 0.7)	0.7 (0.38, 1.34)	< 0.001

Note:

1. Metabolically healthy normal weight ($18.5 \leq \text{BMI} \leq 23.9 \text{ kg/m}^2$) and overweight ($\text{BMI} \geq 24.0 \text{ kg/m}^2$) were defined as participants with metabolically healthy but with different baseline BMI.

2. **Abbreviation:** **M**, male; **F**, female; **BMI**, body mass index; **FBG**, fasting blood glucose; **HbA1c**, glycated hemoglobin A1c; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure; **TC**, total cholesterol; **TG**, total glycerides; **HDL-C**, high-density-lipoprotein cholesterol; **LDL-C**, low-density-lipoprotein cholesterol; **hsCRP**, high sensitivity C-reactive protein; **eGFR**, estimated glomerular filtration rate.

3. *, abnormal distribution, data was represented by medium plus quartile range.

Variables	Metabolically healthy normal weight	Metabolically healthy overweight	P value
eGFR, ml/min/1.73 m ²	112.7±12.3	109.8±12.6	< 0.001
Note:			
1. Metabolically healthy normal weight ($18.5 \leq \text{BMI} \leq 23.9 \text{ kg/m}^2$) and overweight ($\text{BMI} \geq 24.0 \text{ kg/m}^2$) were defined as participants with metabolically healthy but with different baseline BMI.			
2. Abbreviation: M , male; F , female; BMI , body mass index; FBG , fasting blood glucose; HbA1c , glycated hemoglobin A1c; SBP , systolic blood pressure; DBP , diastolic blood pressure; TC , total cholesterol; TG , total glycerides; HDL-C , high-density-lipoprotein cholesterol; LDL-C , low-density-lipoprotein cholesterol; hsCRP , high sensitivity C-reactive protein; eGFR , estimated glomerular filtration rate.			
3. *, abnormal distribution, data was represented by medium plus quartile range.			

During five-year follow up, the cumulative proportion of HBP, IGR, high TC, high TG, high LDL-C, and low HDL-C was 36.4%, 20.1%, 11.2%, 15.3%, 18.4%, and 20.0%, respectively (Fig. 1). Baseline metabolically healthy overweight was associated with high risk of developing high blood pressure [hazards ratio (HR) = 1.23; 95% confidence interval (CI): 1.14, 1.33] and impaired glucose regulation (HR = 1.15; 95% CI: 1.04, 1.28) in fully adjusted model, compared to metabolically healthy normal weight group (Table 2). Baseline healthy overweight was associated with high TC, high TG, high LDL-C, and low HDL-C in age- and sex-adjusted model, however, the association lost significance after further adjusting baseline blood pressure, FBG, HbA1c, and lipid profile except a marginal association between metabolically healthy overweight and high TG (HR = 1.12, 95% CI: 1.001, 1.25, $p = 0.046$) (Table 2).

Table 2

Risk of developing different metabolic abnormalities during follow-up, according to baseline body weight status in 9,836 Chinese adults who were metabolically healthy

Outcome	Metabolically healthy normal weight (BMI < 24.0 kg/m²)	Metabolically healthy overweight (BMI ≥ 24.0 kg/m²)
HBP		
Number of Participants	7,512	2,324
Incident case	2,400	1,177
Age- and sex- adjusted model	Ref (1.0)	1.50 (1.4, 1.61)
Multiple-adjusted model	Ref (1.0)	1.23 (1.14, 1.33)
IGR		
Number of Participants	7,512	2,324
Incident case	1394	594
Age- and sex- adjusted model	Ref (1.0)	1.36 (1.24, 1.51)
Multiple-adjusted model	Ref (1.0)	1.15 (1.04, 1.28)
High TC		
Number of Participants	7,512	2,324
Incident case	836	266
Age- and sex- adjusted model	Ref (1.0)	1.08 (0.94, 1.25)
Multiple-adjusted model	Ref (1.0)	1.03 (0.89, 1.19)
High TG		
Number of Participants	7,512	2,324
Incident case	908	595
Age- and sex- adjusted model	Ref (1.0)	1.79 (1.6, 1.99)
Multiple-adjusted model	Ref (1.0)	1.12 (1.001, 1.25)
High LDL-C		
Number of Participants	7,512	2,324
Incident case	1,264	550

Outcome	Metabolically healthy normal weight (BMI < 24.0 kg/m ²)	Metabolically healthy overweight (BMI ≥ 24.0 kg/m ²)
Age- and sex- adjusted model	Ref (1.0)	1.31 (1.18, 1.45)
Multiple-adjusted model	Ref (1.0)	0.99 (0.89, 1.11)
Low HDL-C		
Number of Participants	7,512	2,324
Incident case	371	238
Age- and sex- adjusted model	Ref (1.0)	1.78 (1.5, 2.1)
Multiple-adjusted model	Ref (1.0)	0.99 (0.83, 1.18)
Dyslipidemia		
Number of Participants	7,512	2,324
Incident case	2,168	1,033
Age- and sex- adjusted model	Ref (1.0)	1.49 (1.38, 1.61)
Multiple-adjusted model	Ref (1.0)	1.07 (0.99, 1.16)
Note:		
1. Abbreviation: HBP , high blood pressure; FBG , fasting blood glucose; HbA1c , glycated hemoglobin A1c; IGR , impaired glucose regulation; TC , total cholesterol; TG , total triglycerides; LDL-C , low-density lipoprotein cholesterol; HDL-C , high-density lipoprotein cholesterol.		
2. Definition: Metabolically healthy was defined as participants without history of high blood pressure, diabetes mellitus, cardiovascular disease, dyslipidemia, and cancer but with normal blood pressure, FBG, HbA1c, TC, TG, LDL-C, and HDL-C. Dyslipidemia was defined if any of the four lipid parameters (TC, TG, LDL-C, and HDL-C) was abnormal.		
2. Criteria: HBP (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg); IGR (FBG ≥ 5.6 mmol/L or HbA1c ≥ 5.7%); high TC, ≥ 5.72 mmol/L; high TG, ≥ 1.7 mmol/L; high LDL-C, ≥ 3.4 mmol/L; low HDL-C, < 0.9 mmol/L in men and < 1.0 mmol/L in women.		
3. Multiple-adjusted model was adjusted for sex, baseline age (y), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), FBG (mmol/L), HbA1c (%), TC (mmol/L), TG (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), estimated glomerular filtration rate (ml/min/1.73 m ²), and high sensitivity C-reactive protein (mg/L).		

We have identified 133 incident cases of CAP during follow up. Compared to those who remained metabolically healthy status, we found that transition to high blood pressure, high TC, high LDL-C, and dyslipidemia during follow up was associated a high likelihood of developing CAP, regardless of baseline

body weight status (Table 3). When considering the transition to impaired glucose regulation, high TG, and low HDL-C, the association only remained in participants with baseline metabolically healthy overweight (Table 3).

Table 3
Risk of incident carotid artery plaque by baseline body weight status and transition to metabolic abnormalities in 9,836 Chinese adults

Models	Metabolically healthy normal weight (n = 7,512, BMI < 24.0 kg/m ²)		Metabolically healthy overweight (n = 2,324, BMI ≥ 24.0 kg/m ²)	
	Stable	Transition to HBP	Stable	Transition to HBP
Number of Participants	5,112	2,400	1,147	1,177
CAP Case	35	50	14	34
Multiple-adjusted model	Ref (1.0)	1.69 (1.06, 2.68)	1.18 (0.62, 2.23)	2.29 (1.35, 3.87)
	Stable	Transition to IGR	Stable	Transition to IGR
Number of Participants	6,118	1,394	1,730	594
CAP Case	56	29	24	24
Multiple-adjusted model	Ref (1.0)	1.17 (0.73, 1.87)	1.11 (0.67, 1.81)	1.95 (1.15, 3.3)
	Stable	Transition to high TC	Stable	Transition to high TC
Number of Participants	6,676	836	2,058	266
CAP Case	61	24	36	12
Multiple-adjusted model	Ref (1.0)	2.04 (1.22, 3.43)	1.33 (0.87, 2.05)	2.34 (1.21, 4.53)
	Stable	Transition to high TG	Stable	Transition to high TG
Number of Participants	6,604	908	1,729	595
CAP Case	69	16	27	21
Multiple-adjusted model	Ref (1.0)	1.23 (0.69, 2.2)	1.08 (0.68, 1.71)	2.27 (1.30, 3.95)
	Stable	Transition to high LDL-C	Stable	Transition to high LDL-C
Number of Participants	6,248	1,264	1,774	550
CAP Case	51	34	31	17

Models	Metabolically healthy normal weight (n = 7,512, BMI < 24.0 kg/m ²)		Metabolically healthy overweight (n = 2,324, BMI ≥ 24.0 kg/m ²)	
Multiple-adjusted model	Ref (1.0)	1.95 (1.20, 3.17)	1.52 (0.95, 2.42)	2.03 (1.11, 3.73)
	Stable	Transition to low HDL-C	Stable	Transition to low HDL-C
Number of Participants	7,403	109	2,252	72
CAP Case	83	2	45	3
Multiple-adjusted model	Ref (1.0)	1.61 (0.39, 6.69)	1.27 (0.86, 1.87)	4.62 (1.4, 15.22)
	Stable	Transition to dyslipidemia	Stable	Transition to dyslipidemia
Number of Participants	5,344	2,168	1,291	1,033
CAP Case	40	45	18	30
Multiple-adjusted model	Ref (1.0)	1.77 (1.11, 2.81)	1.29 (0.73, 2.3)	2.31 (1.35, 3.96)
Note:				
1. Abbreviation: CAP, carotid artery plaque; HBP, high blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; IGR, impaired glucose regulation; TC, total cholesterol; TG, total triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.				
2. Definition: Metabolically healthy was defined as participants without history of high blood pressure, diabetes mellitus, cardiovascular disease, dyslipidemia, and cancer but with normal blood pressure, FBG, HbA1c, TC, TG, HDL-C, and LDL-C. Dyslipidemia was defined if any of the four lipid parameters (TC, TG, LDL-C, and HDL-C) was abnormal.				
3. Criteria: HBP (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg); IGR (FBG ≥ 5.6 mmol/L or HbA1c ≥ 5.7%); high TC, ≥ 5.72 mmol/L; high TG, ≥ 1.7 mmol/L; high LDL-C, ≥ 3.4 mmol/L; low HDL-C, < 0.9 mmol/L in men and < 1.0 mmol/L in women.				
4. Multiple-adjusted model adjusted for sex, baseline age (y), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), FBG (mmol/L), HbA1c (%), TC (mmol/L), TG (mmol/L), LDL-C (mmol/L), HDL-C (mmol/L), estimated glomerular filtration rate (ml/min/1.73 m ²), and high sensitivity C-reactive protein (mg/L).				

We found that the association between the transition to metabolic abnormalities and future risk of CAP was modified by age (all $p < 0.01$), but not sex (**Table e-2**). The results of subgroup analysis, divided by the median of age, confirmed similar association between the transition to metabolic abnormalities and future risk of CAP in participants aged 34 years or more. Excluding participants whose baseline level of hs-CRP was 10 mg/L did not substantially change the association (**Table e-3**). Excluding participants

who were confirmed with metabolic abnormalities once during follow up, the association remained a similar trend. However, the association lost significance in some groups because of small incident cases of CAP (**Table e-4**).

Discussion

In the current study including 9,836 Chinese adults with metabolically healthy at baseline, we found that the transition to metabolic abnormalities were associated with high risk of developing CAP, after adjusting a series of related risk factors, including blood pressure, FBG, HbA1c, lipid profiles, eGFR, and hs-CRP at baseline. If the participants were overweight at baseline but remained metabolically healthy status, the risk of CAP was similar to those whose baseline body weight were normal and remained metabolically healthy during the follow up.

Our results did not support the hypothesis that baseline metabolically healthy obesity was associated with high risk of CAP. Limited to studies in general population with large sample size ($n \geq 1000$), three cross-sectional studies have been performed in Korean adults in which atherosclerosis was assessed by coronary artery calcium score (11, 13, 14). One reported metabolic health was more closely associated with atherosclerosis than obesity (11) while another two found that participants with metabolically healthy obesity had a higher prevalence of atherosclerosis than their metabolically healthy normal weight counterparts (13, 14). However, in the latter study, the association between metabolically healthy obesity and atherosclerosis lost significance after further adjusting LDL-C (14). Our results were consistent with one cross-sectional study in which atherosclerosis was assessed by the same method (ultrasound B model) (7). They found that participants with normal weight and metabolic abnormalities, but not those with overweight but with metabolically healthy, was associated with high prevalence of atherosclerosis (7). As for cohort study, Kim **et al.** (12) reported baseline metabolically healthy overweight (HR = 1.24; 95%CI: 1.12, 1.38) and obesity (HR = 1.54; 95%CI: 1.38, 1.72) were associated with CAP in 6,543 men with a median follow up of 4.2 years. However, as the author acknowledged that including only men were in the study was obvious a limitation. The different definition of metabolically healthy obesity, in combination with ethnicity, population, and statistical method, was blamed for the discrepancies among the studies (16).

Another critical point was the transition from baseline metabolically healthy to metabolic abnormalities, which was previously neglected among previous studies. Chang **et al** (14) also pointed out the association between baseline metabolically healthy obesity and atherosclerosis could be mediated by components of metabolic abnormalities. Further, the Nurse's Health Study reported that 84% of women with obesity and 68% of women with normal-weight were confirmed with metabolic abnormalities after 20 years (24), which indicated that metabolically healthy was unstable and eventually transited to unhealthy status. Lin **et al.** have performed a very interesting cohort study in 6,220 Chinese adults with metabolically healthy (≤ 2 components of metabolic syndrome based on ATP III). Transition to metabolic abnormalities was associated with a odd ratio of 2.52 (95%CI: 1.89, 3.36) for the risk of atherosclerosis compared with their normal weight counterparts (23). Similar to Lin's study, we also confirmed that the

transition was associated with future risk of atherosclerosis. In addition, we found that different types of metabolic abnormalities differed in their effects on the development of atherosclerosis. Abnormalities of blood pressure, TC, and LDL-C were associated a high likelihood of developing atherosclerosis in both metabolically healthy overweight and normal weight groups while the occurrence of abnormalities of glucose regulation, TG, and HDL-C were associated with atherosclerosis only in those who were overweight at baseline.

It is not surprising that we found that age modified the association between the transition and atherosclerosis. In other words, the association remained in elder (≥ 34 years), but not younger participants. Previous studies have proved that the prevalence of both total atherosclerotic related cardiovascular diseases (1) and peripheral artery diseases increased with age (33). We did not find an interaction of sex with the association, which was consistent with previous studies (14, 16).

The strengths of the current study includes more stricter definition of metabolically healthy, a prospective study design, and a fully adjustment of traditional risk factors including blood pressure, FBG, HbA1c, and lipid profile though they were in normal range. However, some limitations must be addressed. First, the history of metabolic diseases was self-reported, which was lower than national prevalence. We thus excluded those with abnormalities at baseline, which could reduce the possibility of misclassification. Second, information about medical intervention, diet, and physical activities was deficient. Anti-coagulant drugs such as aspirin was deficient, which was known to be associated with the development of atherosclerosis (34). Third, all the participants were recruited from those who underwent health checkup in our hospital. It accounted for a small proportion of the total residents; thus, the generalizability of study population was limited. Finally, the number of incident CAP cases was small in the current study. However, this indicates that metabolically healthy status is rare, in particular when it is defined by the absence of any metabolic abnormalities. Multiple-center based cohort studies with a face-to-face interview about history of diseases and medical information were needed to duplicate our results.

Conclusions

The transition from baseline metabolically healthy to metabolic abnormalities was associated with high risk of incident atherosclerosis. Early interventions focusing on both baseline body weight and the occurrence of metabolic abnormalities are meaningful to reduce atherosclerosis related disability and mortality.

Abbreviations

1. **BMI**, body mass index;
2. **CAP**, carotid artery plaque;
3. **eGFR**, estimated glomerular filtration rate;
4. **FBG**, fasting blood glucose;

5. **HbA1c**, glycated hemoglobin A1c;
6. **HBP**, high blood pressure;
7. **HDL-C**, high-density lipoprotein cholesterol;
8. **hs-CRP**, high-sensitivity C-reactive protein;
9. **IGR**, impaired glucose regulation;
10. **LDL-C**, low-density lipoprotein cholesterol;
11. **TC**, total cholesterol;
12. **TG**, total triglycerides;

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethical Committee of Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University. As a de-identified secondary data analysis, patients' consent was waived by the Ethical Committee.

Consent for publication

The corresponding author and all the authors have read and approved the final submitted manuscript, and agreed to conditions noted on the Author Disclosure Form.

No portion of the work has been or is currently under consideration for publication elsewhere. No portion of the manuscript has been published or posted on the Internet.

Availability of data and materials

All the SAS code and re-identified data are available upon reasonable request (xurenying7465@126.com).

Competing interests: All the authors reported no disclosures.

Funding: The study was supported by the grants from Pu Dong Medical Bureau (PW2016D-05).

Authors' contributions: **Tan T.** and **Zhou Y.Q.** analyzed the data and drafted the paper; **Wan Y.P.** and **Fan Z.P.** collected the data; **Xu R.Y.** designed the study, analyzed the data; **Gao X.** gave critical suggestion and final approval of the manuscript.

Acknowledgements: none.

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Figures

Figure 1

The cumulative proportion of different types of metabolic abnormalities during five-year follow up. Abbreviation: HBP, high blood pressure; IGR, impaired glucose regulation; TC, total cholesterol; TG, total triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. Criteria: HBP: systolic blood pressure $\geq$ 130 mmHg and/or diastolic blood pressure $\geq$ 80 mmHg; IGR: fasting blood glucose $\geq$ 5.6mmol/L and/or HbA1c $\geq$ 5.6%; high TC: $\geq$ 5.72mmol/L; high TG: $\geq$ 1.7 mmol/L; high LDL-C: $\geq$ 3.4mmol/L; low HDL-C: <0.9 mmol/L in men and <1.0 mmol/L in women.

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