





BMI, high-sensitivity C-reactive protein and the conversion from metabolically healthy to unhealthy phenotype in Chinese adults: a cohort study

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Abstract

Objective: We performed the cohort study to evaluate the association between BMI, high-sensitivity C-reactive protein (hs-CRP) and the conversion from metabolically healthy to unhealthy phenotype in Chinese adults.

Design: Metabolically healthy was defined as participants without history of metabolic diseases and with normal fasting blood glucose level, glycated Hb A1c level, blood pressure, lipid profile, serum uric acid level and liver ultrasonographic findings at baseline. Participants were either classified into normal weight ($18.5 \leq \text{BMI} < 24.0 \text{ kg/m}^2$) and overweight ($\text{BMI} \geq 24.0 \text{ kg/m}^2$) based on baseline BMI, or low ($< 1 \text{ mg/l}$) and high ($\geq 1 \text{ mg/l}$) groups based on baseline hs-CRP. The conversion from metabolically healthy to unhealthy phenotype was deemed if any of the metabolic abnormalities had been confirmed twice or more during 5 years of follow-up.

Results: Included were 4855 (1942 men and 2913 women, aged 36.0 ± 8.9 years) metabolically healthy Chinese adults. We identified 1692 participants who converted to metabolically unhealthy phenotype during the follow-up. Compared with their counterparts, the adjusted hazards ratio of the conversion was 1.19 (95% CI 1.07, 1.33) for participants with overweight, while it was 1.15 (95% CI 1.03, 1.29) for those with high hs-CRP level ($\geq 1 \text{ mg/l}$). Further adjustment of hs-CRP did not materially change the association between BMI and the conversion. However, the association between hs-CRP and the conversion was not significant after further adjustment of BMI. The sensitivity analysis generated similar results to main analysis.

Conclusion: BMI was associated with the risk of the conversion from metabolically healthy to unhealthy status in Chinese adults.

Keywords
Metabolically healthy
BMI
High-sensitivity C-reactive protein
Metabolic unhealthy
Adults

Although more and more efforts have been made to curb the epidemic of obesity, the global prevalence of obesity keeps growing slowly and maintains at high level in many countries⁽¹⁾. Age-standardised prevalence of obesity among American adults increased from 33.7% in 2007–2008 to 39.6% in 2015–2016⁽²⁾. The estimated annual costs of obesity were approximately \$US 2 trillion⁽³⁾.

Individuals with excess body weight are believed to be benefited from early diet and lifestyle intervention⁽⁴⁾.

However, some of these individuals are reluctant to initiate these interventions because evidences showed that they were not always associated with increased risk of cardio-metabolic complications and mortality^(5,6). The unique population was named as metabolically healthy overweight, although the widely accepted definition was absent^(7,8). However, some knowledge gaps need to be addressed. First, it is doubtful to define participants with one type of metabolic abnormality as metabolically

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healthy^(9–15). Further, fatty liver⁽¹⁶⁾ and hyperuricaemia⁽¹⁷⁾, which were closely associated with cardiovascular events and usually considered as metabolic abnormalities, were not included in the metabolically healthy obesity (MHO) criteria in most of the previous studies^(9–15,18–20). Second, what contributes to the conversion from metabolically healthy to unhealthy condition remained uncertain. The prevalence of conversion from metabolically healthy to unhealthy phenotype ranges from 28 to 84 %^(9–15,18–20), and mixed results are generated to determine the factors, such as BMI, contributing to the conversion among existing studies. Some^(9,12,14,15), but not all^(10,11), reported that BMI was associated with high risk of conversion.

Therefore, we performed the current cohort study to evaluate the association between BMI and the conversion from metabolically healthy to unhealthy phenotype in about 5000 metabolically healthy Chinese adults during 5 years of follow-up. The association between inflammatory status, assessed by high-sensitivity C-reactive protein (hs-CRP), and the conversion was also evaluated because hs-CRP contributed to metabolic abnormalities^(21,22). Further, a meta-analysis suggested that hs-CRP might not be an independent risk factor⁽²³⁾ and hs-CRP and BMI could be jointly associated with insulin resistance⁽²⁴⁾ and metabolic diseases⁽²⁵⁾.

Materials and methods

Study population

All the participants were recruited from the Health Management Center in a teaching hospital from 1 January 2013 to 31 December 2018. All adult (≥ 18 years old) individuals receiving routine health check-up at our Health Management Center were eligible for the study. An initial recruitment resulted in an identification of 110 859 participants. Body weight, glycated Hb A1c (HbA1c, normal range $< 6\%$), fasting blood glucose (FBG), blood pressure (systolic blood pressure (normal range < 130 mmHg) and diastolic blood pressure (normal range < 80 mmHg)), lipid profile (TAG (normal range < 1.7 mmol/l), total cholesterol (< 5.72 mmol/l), LDL-cholesterol (normal range < 3.4 mmol/l) and HDL-cholesterol (normal range ≥ 0.9 mmol/l in men and ≥ 1.0 mmol/l in women)), serum uric acid (normal range < 416 $\mu\text{mol/l}$ in men and < 357 $\mu\text{mol/l}$ in women) and liver B ultrasonography were annually assessed throughout the study (2013–2018). Hs-CRP was assessed at baseline (2013). The history of hypertension, diabetes/impaired fasting glucose, dyslipidaemia, gout/hyperuricaemia and CVD (stroke, haemorrhage, coronary artery bypass grafting, stent surgery and ischaemic infarction) was collected via a self-report questionnaire.

Metabolically healthy was defined as participants with no history of metabolic diseases, normal FBG level, HbA1c level, blood pressure, lipid profile, serum uric acid

level and liver ultrasonographic findings at baseline⁽²⁶⁾. To recruit metabolically healthy participants, we first excluded participants with history of metabolic diseases and cancer (n 10 089) and those with baseline metabolic abnormalities (high blood pressure (n 37 563), impaired glucose regulation (n 14 610), dyslipidaemia (n 14 155), hyperuricaemia (n 2885)⁽¹⁶⁾ and fatty liver (n 134)⁽¹⁷⁾). Then, we excluded participants with low baseline BMI (≤ 18.4 kg/m², n 2570) and very high level of hs-CRP (≥ 10 mg/l, n 294)⁽²⁷⁾. Finally, we excluded participants lost to follow-up (n 13 378) and with missing data during the follow-up (n 10 259). Because there were only thirty-eight aged participants (≥ 65 years), we further excluded them. Included were 4855 (1942 men and 2913 women) metabolically healthy Chinese adults with mean age of 36.0 ± 8.9 years (Fig. 1). Participants included in the study tended to be younger and 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 (see online supplementary material, Supplemental Table S1). The study protocol was approved by the Ethical Committee. As a de-identified secondary data analysis, patients' consent was waived by the Ethical Committee.

Exposure

In the current study, baseline BMI and hs-CRP were considered as the exposures. Body weight (to the nearest 0.5 kg) and height (to the nearest 0.5 cm) were measured in standing position without shoes and in light clothing, using an electronic scale (SK-CK; Shuang Jia Company). BMI was calculated by body weight (kg) divided by height square (m²). Participants were classified into normal weight ($18.5 \leq \text{BMI} < 24.0$ kg/m²) or overweight (BMI ≥ 24.0 kg/m²) groups based on the criteria for Chinese adults⁽²⁸⁾.

Venous blood samples were drawn and transfused into vacuum tubes containing EDTA in the morning after participants were fasted for at least 6 h. The concentration of hs-CRP was measured by the immunoturbidimetric method (CardioPhase hsCRP kit; Siemens Healthcare Diagnostics Products GmbH). The lower limit of detection was 0.01 mg/l. The intra-assay CV was 7.6 % and the inter-assay CV was 4.0 %. All the participants were classified into low risk (< 1.0 mg/l) and high risk (≥ 1.0 mg/l) groups based on baseline hs-CRP⁽²⁹⁾.

Baseline BMI and hs-CRP had a significant interaction, in relation to the risk of the conversion (P interaction was tested by likelihood-ratio tests where BMI and hs-CRP were categorised as follows: BMI < 24.0 kg/m² *v.* BMI ≥ 24.0 kg/m² and hs-CRP < 1 *v.* ≥ 1 mg/l, $P_{\text{for interaction}} = 0.005$). We further classified the participants into four groups based on both baseline BMI and hs-CRP status as follows: normal body weight – low-risk group, BMI < 24.0 kg/m² and hs-CRP < 1.0 mg/l; normal body weight – high-risk group, BMI < 24.0 kg/m² and hs-CRP ≥ 1 mg/l;

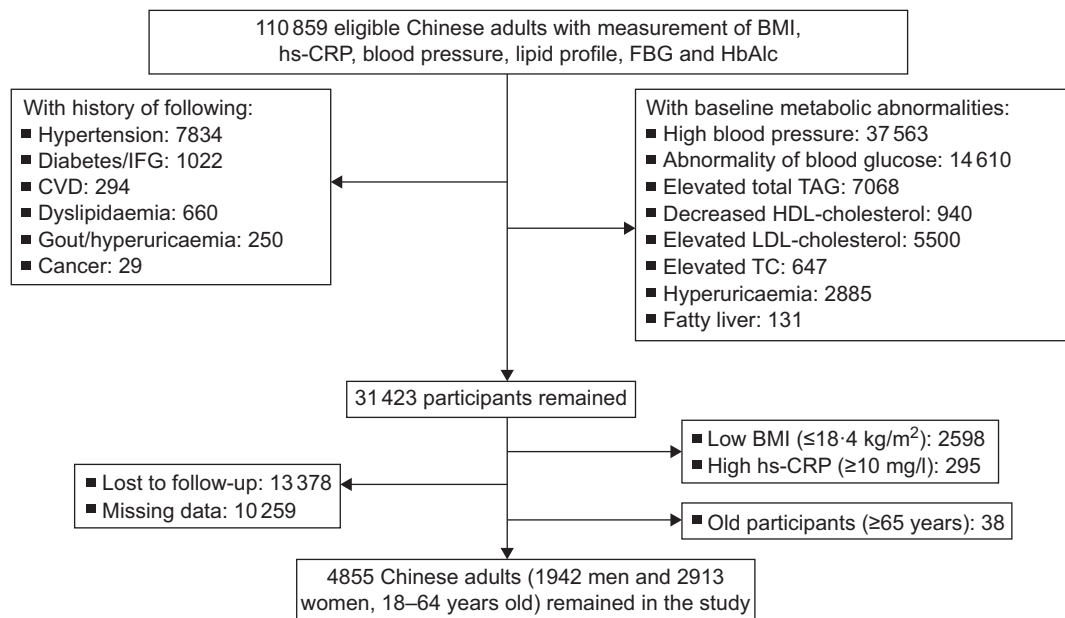


Fig. 1 The process of sample recruitment. Criteria: high blood pressure, systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg; abnormality of blood glucose, FBG ≥ 5.6 mmol/l and/or HbA1c $\geq 5.6\%$; elevated TAG, ≥ 1.7 mmol/l; elevated TC, ≥ 5.72 mmol/l; elevated LDL-cholesterol, ≥ 3.4 mmol/l; decreased HDL-cholesterol, <0.9 mmol/l in men and <1.0 mmol/l in women; hyperuricaemia, serum uric acid ≥ 416 μ mol/l in men and ≥ 357 μ mol/l in women. Fatty liver was confirmed by the ultrasound B model. CVD included stroke, haemorrhage, coronary artery bypass grafting, stent surgery and ischaemic infarction. hs-CRP, high-sensitivity C-reactive protein; FBG, fasting blood glucose; HbA1c, glycated Hb A1c; IFG, impaired fasting glucose; TC, total cholesterol

overweight – low-risk group, BMI ≥ 24.0 kg/m² and hs-CRP <1 mg/l and overweight – high-risk group, BMI ≥ 24.0 kg/m² and hs-CRP ≥ 1.0 mg/l.

Outcomes

An automatic analyser (Roche 701 Bioanalyzer; Roche) was used to measure FBG with the hexokinase/glucose-6-phosphate dehydrogenase method. The CV using blind quality control specimens was 2.0%. The concentration of HbA1c was measured by HPLC, using the fully automated VARIANT™ II Hemoglobin Testing System (Bio-Rad). The measurement range was between 2.0 and 18.0%. Blood pressure was measured twice using an automatic blood pressure metre (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. Total cholesterol, TAG, HDL-cholesterol, LDL-cholesterol, alanine transferase, aspartate transferase, creatinine and uric acid were measured by an automatic biochemical analyser (Roche 701 Bioanalyzer; Roche). The estimating glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2-level race equation⁽³⁰⁾. All the measurements were completed in the clinical laboratory of our hospital.

Metabolically healthy was defined as participants with no history of metabolic diseases, free of metabolic abnormalities and normal liver ultrasonographic findings

at baseline⁽²⁶⁾. Conversion from baseline metabolically healthy to unhealthy phenotype (outcome) was deemed if any of the following metabolic abnormalities were at least double confirmed during subsequent 5 years of follow-up: high blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg)⁽³¹⁾, glucose abnormality (FBG ≥ 5.6 mmol/l or HbA1c $\geq 5.7\%$)⁽³²⁾, dyslipidaemia (elevated total glycerides ≥ 1.7 mmol/l, elevated total cholesterol ≥ 5.72 mmol/l, elevated LDL-cholesterol ≥ 3.4 mmol/l, decreased HDL-cholesterol <0.9 mmol/l in men and <1.0 mmol/l in women)⁽³³⁾, hyperuricaemia (serum uric acid ≥ 416 μ mol/l in men and ≥ 357 μ mol/l in women)⁽³⁴⁾ and fatty liver⁽³⁵⁾.

Statistical analysis

Data were presented as mean and SD 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.). 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 1 January 2014 to either the first onset date of the conversion or the end of follow-up (31 December 2018), whichever came first.

We used the proportional Cox regression model to evaluate the association between baseline BMI, hs-CRP and the conversion from metabolically healthy to



unhealthy phenotype. We adjusted the potential confounders in different models: model 1, adjusting for age (years) and sex and model 2, further adjusting for baseline systolic blood pressure (mmHg), diastolic blood pressure (mmHg), FBG (mmol/l), HbA1c (%), total cholesterol (mmol/l), TAG (mmol/l), LDL-cholesterol (mmol/l), HDL-cholesterol (mmol/l), alanine transferase (U/l), aspartate transferase (U/l), uric acid ($\mu\text{mol/l}$) and estimating glomerular filtration rate ($\text{ml/min per } 1.73 \text{ m}^2$). We further adjusted the baseline hs-CRP when considering the association between BMI and the conversion while baseline BMI when considering the association between hs-CRP and the conversion in model 3.

Likelihood-ratio tests were conducted to examine statistical interactions between baseline BMI and sex, and age, in relation to the conversion 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 four sensitivity analyses in model 2. First, we censored participants whose baseline level of hs-CRP was 3.0 mg/l or more⁽²⁹⁾. Then, we censored participants whose BMI was 28.0 kg/m^2 or more⁽²⁸⁾. Third, we censored participants who were confirmed with the conversion either in 2014 or in 2015 to alleviate the potential distraction of baseline characteristics. At last, we replaced baseline BMI by cumulative average of BMI (the average of all the measurements during the follow-up) as the exposure. The participants were classified into normal weight ($\text{BMI} < 24.0 \text{ kg/m}^2$) or overweight ($\text{BMI} \geq 24.0 \text{ kg/m}^2$) groups based on the criteria for Chinese adults⁽²⁸⁾.

Results

The mean age and BMI were 36.0 ± 8.9 years and $22.2 \pm 2.4 \text{ kg/m}^2$, respectively, while median hs-CRP level was 0.38 mg/l (inter-quartile range $0.2, 0.76 \text{ mg/l}$). There were significant differences in all the baseline characteristics except total cholesterol level (Table 1).

We identified 1692 (34.9%) participants who experienced the conversion from baseline metabolically healthy to unhealthy phenotype during 5 years of follow-up. Compared with their counterparts, the adjusted hazards ratio (HR) was 1.04 (95% CI 1.02, 1.07) for each unit (1.0 kg/m^2) increase of BMI to the conversion, while it was 1.12 (95% CI 1.02, 1.22) for each mg/l increase of hs-CRP level, after adjustment of age, sex, baseline blood pressure, FBG, HbA1c, lipid profile, alanine transferase, aspartate transferase, uric acid and estimating glomerular filtration rate (Table 2, model 2). Further adjustment of hs-CRP did not materially change the association between BMI and the risk of the conversion (adjusted HR = 1.04 for each unit increase of BMI, 95% CI 1.01, 1.07). However, the association between hs-CRP and the risk of the conversion was not significant after further adjustment of BMI (adjusted

HR = 1.09 for each mg/l increase of hs-CRP level, 95% CI 0.99, 1.19) (Table 2, model 3).

Compared with participants with normal weight and low level of hs-CRP, participants with overweight and high level of hs-CRP were associated with the highest risk of the conversion (adjusted HR 1.35, 95% CI 1.14, 1.59). Participants with overweight but low level of hs-CRP were also associated with higher risk of the conversion (adjusted HR 1.16, 95% CI 1.02, 1.32). However, the association was not significant in the reverse scenario (HR 1.11, 95% CI 0.95, 1.29) (Table 3, model 2).

We did not find significant interaction between BMI and sex, and age, in relation to the risk of the conversion (all $P > 0.05$, see online supplementary material, Supplemental Table S2). Excluding participants whose baseline hs-CRP level was 3 mg/l or more ($n = 185$), or participants who experienced the conversion in the first 2 years (2014 and 2015) ($n = 748$), and using cumulative average of BMI as the exposure generated similar results to the main analysis (see online supplementary material, Supplemental Table S3).

Discussion

In the current cohort study, we found that baseline BMI was associated with the risk of the conversion from metabolically healthy to unhealthy phenotype in about 5000 Chinese adults, after adjustment of age, sex, baseline blood pressure, FBG, HbA1c, lipid profile, alanine transferase, aspartate transferase, uric acid and estimating glomerular filtration rate. Compared with participants with normal body weight and low level of hs-CRP, participants with overweight and high level of hs-CRP were associated with the highest risk of the conversion.

A recent large-scale cohort study ($n = 121\,701$) confirmed that most of the women with obesity moved from metabolically healthy to unhealthy condition after 20 years of follow-up⁽¹⁹⁾. However, the factors contributing to the conversion remained unclear. Our results, consisted with the previous studies^(12,15) focusing on participants with obesity and general population⁽¹⁴⁾, confirmed that BMI was associated with the risk of conversion. Moussa *et al.*⁽¹²⁾ recruited 231 399 metabolically healthy patients with a recorded BMI of 35 kg/m^2 or greater from the Clinical Practice Research Datalink, and they reported that participants with higher BMI ($50\text{--}60 \text{ kg/m}^2$) were in higher risk of conversion to unhealthy phenotype, compared with participants with relatively lower BMI ($35\text{--}40 \text{ kg/m}^2$). Participants with the highest BMI ($\geq 60 \text{ kg/m}^2$) were associated with the shortest duration of stable MHO⁽¹²⁾. Hamer *et al.*⁽¹⁵⁾ reported metabolically healthy participants with obesity were four times as likely to convert to metabolically unhealthy phenotype compared with healthy participants with normal weight. Another cohort study included

Table 1 Baseline characteristics across different BMI and high-sensitivity C-reactive protein (hs-CRP) groups in 4855 metabolically healthy Chinese adults*

Groups	NBW – low risk		NBW – high risk		Overweight – low risk		Overweight – high risk		P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Sample	3261		545		726		323		–
Age (years)	35.7	8.7	35.7	9.0	37.0	9.4	36.9	9.2	0.001
Sex (%)									<0.001
Men	32.5		44.2		64.5		53.6		
Women	67.5		55.8		35.5		46.4		
hs-CRP (mg/l)									<0.001
Median	0.28		1.59		0.41		1.60		
Inter-quartile range	0.17, 0.47		1.22, 2.56		0.26, 0.61		1.21, 2.71		
BMI (kg/m ²)	21.2	1.5	21.5	1.4	25.5	1.3	26.0	1.9	<0.001
SBP (mmHg)	107.9	9.6	109.0	±9.0	112.7	9.0	113.1	8.4	<0.001
DBP (mmHg)	67.0	7.0	67.9	6.7	69.5	6.1	69.5	6.7	<0.001
FBG (mmol/l)	4.8	0.4	4.8	0.4	4.8	0.4	4.8	0.4	<0.001
HbA1c (%)	5.1	0.3	5.1	0.3	5.2	0.3	5.2	0.3	<0.001
ALT (U/l)									<0.001
Median	12		13		17		18		
Inter-quartile range	10, 17		10, 19		12, 23		13, 25		
AST (U/l)									<0.001
Median	16		16		17		18		
Inter-quartile range	14, 19		14, 20		15, 20		15, 21		
TC (mmol/l)	4.4	0.6	4.4	0.6	4.4	0.6	4.5	0.6	0.380
TAG (mmol/l)	0.8	0.3	0.9	0.3	1.0	0.3	1.0	0.3	<0.001
HDL-cholesterol (mmol/l)	1.5	0.3	1.4	0.3	1.4	0.3	1.3	0.3	<0.001
LDL-cholesterol (mmol/l)	2.4	0.5	2.5	0.5	2.6	0.5	2.6	0.5	<0.001
Uric acid (μmol/l)	274.1	57.2	293.4	57.1	310.8	59.6	311.8	57.1	<0.001
eGFR (ml/min per 1.73 m ²)	113.8	11.6	114.1	11.1	111.1	11.4	111.9	11.9	<0.001

NBW, normal body weight; HbA1c, glycated Hb A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated Hb A1c; ALT, alanine transferase; AST, aspartate transferase; TC, total cholesterol; eGFR, estimating glomerular filtration rate.

*Criteria: NBW – low risk, BMI < 24.0 kg/m² and hs-CRP < 1.0 mg/l; NBW – high risk, BMI < 24.0 kg/m² and hs-CRP ≥ 1 mg/l; overweight – low risk, BMI ≥ 24.0 kg/m² and hs-CRP < 1 mg/l; overweight – high risk, BMI ≥ 24.0 kg/m² and hs-CRP ≥ 1.0 mg/l.

Table 2 Adjusted hazards ratios (HR) and 95 % CI for the risk of the conversion from metabolically healthy to unhealthy phenotype, across different BMI and high-sensitivity C-reactive protein (hs-CRP) groups during 5 years of follow-up among 4855 metabolically healthy Chinese adults

Baseline BMI	–	Normal (<24.0 kg/m ²)	Overweight (≥24.0 kg/m ²)		Per unit of BMI		<i>P</i> _{for linear trend}
			HR	95 % CI	HR	95 % CI	
	Sample number	3806	1049				
	Case number	1150	542				
	Model 1*	Ref. (1)	1.66	1.46, 1.80	1.13	1.10, 1.16	<0.001
	Model 2†	Ref. (1)	1.19	1.07, 1.33	1.04	1.02, 1.07	0.002
	Model 3‡	Ref. (1)	1.16	1.04, 1.30	1.04	1.01, 1.07	0.008
Baseline hs-CRP	–	Low risk (<1 mg/l)	High risk (≥1 mg/l)				
	Sample number	3987	868				
	Case number	1300	392				
	Model 1*	Ref. (1)	1.40	1.25, 1.57	1.3	1.19, 1.41	<0.001
	Model 2†	Ref. (1)	1.15	1.03, 1.29	1.12	1.02, 1.22	0.017
	Model 3‡	Ref. (1)	1.11	0.99, 1.25	1.09	0.99, 1.19	0.074

*Model 1, adjusting for age (years) and sex.

†Model 2, adjusting for age (years) and sex, and further baseline systolic blood pressure (mmHg), diastolic blood pressure (mmHg), fasting blood glucose (mmol/l), HbA1c (%), total cholesterol (mmol/l), TAG (mmol/l), LDL-cholesterol (mmol/l), HDL-cholesterol (mmol/l), alanine transferase (U/l), aspartate transferase (U/l), uric acid (μmol/l) and estimating glomerular filtration rate (ml/min per 1.73 m²).

‡Model 3, adjusting for variables in model 2 and further baseline hs-CRP (mg/l) for BMI as well as BMI (kg/m²) for hs-CRP.

Table 3 Adjusted hazards ratios (HR) and 95 % CI for the risk of the conversion from metabolically healthy to unhealthy status, across different groups divided by baseline BMI and high-sensitivity C-reactive protein (hs-CRP) during 5 years of follow-up among 4855 metabolically healthy Chinese adults*

Groups	NBW – low risk	NBW – high risk		Overweight – low risk		Overweight – high risk	
		HR	95 % CI	HR	95 % CI	HR	95 % CI
Sample number	3261	545		726		323	
Case number	946	204		354		188	
Model 1†	Ref. (1)	1.28	1.10, 1.49	1.55	1.37, 1.76	2.04	1.74, 2.39
Model 2‡	Ref. (1)	1.11	0.95, 1.29	1.16	1.02, 1.32	1.35	1.14, 1.59

*Criteria: NBW – low risk, BMI < 24.0 kg/m² and hs-CRP < 1.0 mg/l; NBW – high risk, BMI < 24.0 kg/m² and hs-CRP ≥ 1 mg/l; overweight – low risk, BMI ≥ 24.0 kg/m² and hs-CRP < 1 mg/l; overweight – high risk, BMI ≥ 24.0 kg/m² and hs-CRP ≥ 1.0 mg/l.

†Model 1, adjusting for age (years) and sex.

‡Model 2, adjusting for age (years) and sex, and further baseline systolic blood pressure (mmHg), diastolic blood pressure (mmHg), fasting blood glucose (mmol/l), HbA1c (%), total cholesterol (mmol/l), TAG (mmol/l), LDL-cholesterol (mmol/l), HDL-cholesterol (mmol/l), alanine transferase (U/l), aspartate transferase (U/l), uric acid (μmol/l) and estimating glomerular filtration rate (ml/min per 1.73 m²).

27 478 metabolically healthy Japanese participants with similar BMI (21.4 ± 2.0 kg/m² for normal weight group and 26.8 ± 1.7 kg/m² for obesity group) to our study, and the results also showed that high baseline BMI was a risk factor for the conversion (HR 1.11; 95 % CI 1.02, 1.21) to unhealthy phenotype⁽¹⁴⁾. However, two cohort studies, also focusing on participants with obesity (BMI ≥ 30 kg/m²), did not confirm the association between BMI and the risk of conversion^(10,11). Except for the absence of standard definition, the differences in baseline BMI and study population might be plausible explanations. The opposite evidences were generated from the studies^(10,11) including participants with obesity, while our study and two other studies^(14,15) included both participants with obesity and with normal body weight. In the study including only participants with obesity, mean BMI at baseline was 38.8 kg/m², and participants with

BMI of 50–60 kg/m² were associated with high risk of conversion⁽¹²⁾. It was obviously higher than those in two opposite studies^(10,11).

Our study found that hs-CRP was also associated with the risk of the conversion; however, the association lost after further adjustment of BMI. A cross-sectional study supported our findings. They reported that the level of hs-CRP was similar between metabolically healthy participants with and without the metabolic syndrome⁽²²⁾. Kouvari *et al.*⁽¹¹⁾ reported the high level of hs-CRP was associated with metabolically healthy participants with obesity; however, the results were based on unadjusted analysis. The results indicated that the association between baseline body weight status (assessed by BMI) and the development into unhealthy condition was mediated by low-grade systemic inflammation (assessed by hs-CRP). The mechanism between BMI and the conversion was unclear; however, it

might share the same pathway between obesity and metabolic diseases, in which inflammation⁽³⁶⁾ and dysfunction of adipose tissue⁽³⁷⁾ could play important roles.

The strength of the current study includes its strictest definition of metabolically healthy ('zero' risk factors of metabolic abnormalities including blood pressure, glucose metabolism, lipid profile, serum uric acid level and liver ultrasonography) and double confirmation of metabolic abnormalities during the follow-up, which provided greater breadth of insights regarding accurate estimates of metabolic outcomes of the MHO phenotype. Our study also has some limitations. First, the current study focused on the baseline measure of CRP and neglected long-term change. The concentration of CRP changes in life⁽³⁸⁾. Temporary fluctuations and changes in CRP levels over time may result in underestimation of the true association between exposure and outcome. Second, the participants in the current study were recruited from healthy examination in our hospital, which could not represent the general population in Shanghai city. Generalisability of our findings is thus limited. Second, information on other lifestyle factors and behaviours (e.g., physical activity and diet), which have been identified as modifiable factors for carotid artery plaque (CAP)⁽³⁹⁾, was not collected. Waist circumference, which might be closely associated with metabolic abnormalities⁽⁴⁰⁾, was also not collected, which could result in overestimation of the association between BMI and the risk of conversion. Third, behaviour habits such as smoking were not included in the analysis. The self-report prevalence of smoking in this population was rather low (1%), and we thus did not include smoking variable in the model. Excluding those self-reported smokers did not materially change significant results (data not shown). Finally, we could not exclude the possible collinearity because there was a significant correlation between baseline BMI and hs-CRP (coefficient was 0.137 in men and 0.208 in women controlling for baseline age, both $P < 0.01$). However, the variance inflation factor was 1.172 for BMI (normal *v.* overweight) and 1.058 for hs-CRP (<1 *v.* ≥ 1 mg/l), which showed that the effects of collinearity might be slight.

Conclusions

BMI was associated with the risk of the conversion from metabolically healthy to unhealthy status in Chinese adults. Metabolically healthy participants with overweight and obesity are necessary to initiate dietary and behaviour intervention, facilitating to maintain a stable metabolically healthy condition. Although the association between baseline hs-CRP and the risk of the conversion from metabolically healthy to unhealthy status lost when further adjusting for baseline BMI, the role of hs-CRP should not be underestimated. BMI and hs-CRP were jointly associated with the risk of conversion from metabolically healthy to unhealthy status.

Data availability

The SAS code and data that support the findings of the current study are available from the first author upon reasonable request.

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Supplementary material

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