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Synergism between the metabolic syndrome components and cancer incidence: results from a prospective nested case–control study based on the China Health and Retirement Longitudinal Study (CHARLS)

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ABSTRACT

Objectives Synergism between the metabolic syndrome (MetSyn) components and cancer incidence still remains inconclusive. We aimed to investigate the unique or joint role of MetSyn components in cancer onset.

Design We conducted a prospective nested case–control study based on the China Health and Retirement Longitudinal Study.

Setting An ongoing national representative longitudinal study included follow-up survey of people aged 45 years and older and their partners living in private households in China.

Participants There were 17 708 individuals included at baseline. A total of 306 incident cancers was identified during the follow-up. For every case, we used incidence-density sampling to match three concurrent cancer-free controls by age, sex, and both duration and calendar time of follow-up. Exposure of interest was any MetSyn diagnosis at baseline.

Results We observed elevation in cancer risk associated with MetSyn in a significant way when the number of MetSyn components was over three (OR: 1.88; 95% CI: 1.19 to 2.97), or when components contained any of elevated triglycerides (OR: 1.61; 95% CI: 1.05 to 2.48), reduced high-density lipoprotein (HDL) cholesterol (OR: 2.33; 95% CI: 1.40 to 3.86) or elevated blood pressure (OR: 1.65; 95% CI: 1.04 to 2.59) after consistent multiple adjustments in different models. The highest cancer risk was in the female reproductive system and breast cancer (OR: 4.22; 95% CI: 1.62 to 10.95) followed by digestive system (OR: 1.67; 95% CI: 1.11 to 2.53). Sensitivity analyses showed similar results after first follow-up was excluded. However, any unique MetSyn component was not associated with increased cancer risk. Interestingly, the reduced HDL was observed to be widely associated with over twofold increased risk of cancer, only when together with other MetSyn components.

Conclusion MetSyn components, in a collaborative manner rather than its unique component, were associated with elevated cancer risk. Not only obesity but even subtle metabolic disturbances may give rise to cancer.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A series of covariables was collected so that the multiple adjustments became available.
⇒ A sensitivity analysis was conducted to avoid reverse causality.
⇒ Several multiple models were used to ensure the replicability of the results.
⇒ Relatively short period of follow-up limited our ability to identify more cancer cases, which could have hindered the statistical power for the stratified analyses by the sites of cancer.
⇒ Asynchronous occurrence of metabolic syndrome and cancer still could not be totally excluded because of self-report, although we had reduced the chance as far as possible by setting a strict time point for participants to answer their diagnosis.

INTRODUCTION

The metabolic syndrome (MetSyn) is characterised by multimorbidity related to cardiovascular diseases and type 2 diabetes mellitus, including central obesity, hypertension, dyslipidaemia, hyperglycaemia and insulin resistance, as well as other conditions such as proinflammatory state and prothrombotic state.[1 2] The definition of MetSyn had been evolving over history and finally the 'harmonised' definition of MetSyn was introduced by the International Diabetes Federation (IDF), National Institutes of Health (NIH), American Heart Association (AHA), International Atherosclerosis Society, World Heart Federation and the International Association for the Study of Obesity in 2009, in an effort to provide more consistency in both clinical care and research of patients with MetSyn.[3] This frequently referred definition[4] stated that a diagnosis of MetSyn is made when any three of the five following risk factors are present:

elevated triglycerides (TG) (≥150 mg/dL (≥1.7 mmol/L), decreased high-density lipoprotein cholesterol (HDL-C) (male: <40 mg/dL (<1.0 mmol/L); female: <50 mg/dL (<1.3 mmol/L)), elevated blood pressure (BP) (systolic BP (SBP) ≥130 mm Hg, and/or diastolic BP (DBP) ≥85 mm Hg), elevated fasting glucose (FPG (fasting plasma glucose) ≥100 mg/dL (≥5.6 mmol/L)) and enlarged waist circumference (WC) (male: ≥90 cm, female: ≥80 cm) specific to countries and population.

Recently, there is cumulating evidence that MetSyn with its hormonal and systemic effects could increase the susceptibility to various cancers.[5–7] A biological mechanism underlying this association had evolved to at least include the growth hormone deregulation, cellular crosstalk, vascular integrity factors, proximal adipose tissue inflammation and disturbed metabolism.[6 8–10] However, the effect of the unique or joint components of MetSyn on cancer risk and in what ways the proposed association was impacted by follow-up periods and types of cancer still lack epidemiological evidence to our knowledge.

In the present study, we aimed to prospectively examine whether the risk of incident cancer was elevated secondary to unique or combined MetSyn components, with particular interests in exploring the number threshold and combinative ways of MetSyn components. This will be able to aid in identifying individuals at risk and provide thoughts for clinical management and treatment of co-diagnosis of MetSyn with cancer.

METHODS

Data

The China Health and Retirement Longitudinal Study (CHARLS) is an ongoing national representative longitudinal study administered by the National School for Development (China Centre for Economic Research). CHARLS included follow-up survey of people aged 45 years and older and their partners living in private households in China. Its main goal is to provide a data resource on health and socioeconomic status among older adults. The cohort profile was depicted in a previous publication.[11] The CHARLS included examinations performed every 2 years for a total of four waves from 2011 to 2018 until now. The first national baseline survey of the CHARLS was fielded between June 2011 and March 2012 and involved 17 708 respondents who were chosen randomly with a probability proportional to scale in 450 villages/resident committees, 150 counties/districts and 28 provinces. The respondents were interviewed face-to-face in their homes via computer-assisted personal interviewing technology.[11–13]

The present study used the baseline data from 2011 and follow-up data at 2013, 2015 and 2018 to investigate the association between MetSyn and its components with the onset of incident cancer. A total of 17 297 individuals met the inclusion criteria at baseline and was included in the follow-ups. There were 16 109, 15 062 and 13 522 respondents retrieved at the first wave at 2013, the second wave at 2015, and the third wave at 2018, respectively (figure 1).

Definition of cancer

All participants were asked: 'Have you ever been diagnosed with cancer or malignant tumour (excluding minor skin cancers) by a doctor?' Participants with an affirmative answer were further asked: 'In which location of your body do you have cancer? Including the origins and metastasis of tumour (circle all that apply): (1) brain; (2) oral cavity; (3) larynx; (4) other pharynx; (5) thyroid; (6) lung; (7) breast; (8) oesophagus; (9) stomach; (10) liver; (11) pancreas; (12) kidney; (13) prostate; (14) testicle; (15) ovary; (16) cervix; (17) endometrium; (18) colon or rectum; (19) bladder; (20) skin; (21) non-Hodgkin's lymphoma; (22) leukaemia; (23) other location'. Participants with affirmative answer were classified as having cancer. Furthermore, participants who died during the study period and with cancer listed as the cause of death were also identified as having incident cancer.[11 13]

Selection of cancer-free concurrent control and matching

During three waves of the follow-up, cancer occurred in 306 participants. For every incident cancer, we used incidence-density sampling to randomly choose and match three cancer-free concurrent controls by age, sex, and both duration and calendar time of follow-up.[14] Distribution of comorbidities (Charlson Comorbidity

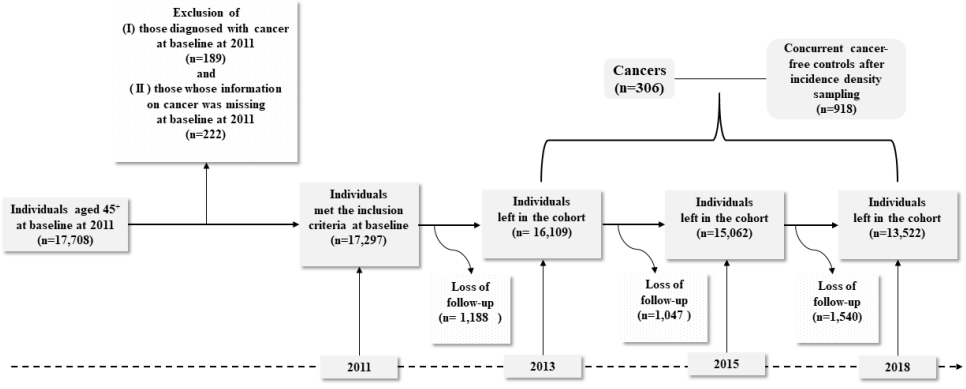

Figure 1 Flow diagram of study participants.

Index) was balanced between cases and controls after matching (X^2=0.8634, p=0.649).

Exposure of interest (MetSyn) and covariates

The CHARLS baseline questionnaire includes information on demographics, socioeconomic factors, lifestyle and health-related behaviours as well as self-reported chronic illness. Biochemical indexes related to MetSyn diagnosis were recorded and defined as below. BP was measured three times with Omron HEM-7200 Monitor according to the protocol, and the average of the three readings was used. The anthropometric measurements also were assessed. Hypertension was defined as SBP ≥130 mm Hg and/or DBP ≥85 mm Hg, and/or self-reported hypertension/drug treatment for hypertension. Obesity was defined according to the WC measured, and the average of the three readings was used (Chinese standard: male, ≥90 cm; female, ≥80 cm). Diabetes was defined as FPG ≥100 mg/dL (≥5.6 mmol/L), and/or self-reported history of diabetes/drug treatment for elevated glucose. The cut-off point of elevated TG was 150 mg/dL (≥1.7 mmol/L). The reduced HDL-C was defined by gender (male: <40 mg/dL (<1.0 mmol/L); female: <50 mg/dL (<1.3 mmol/L)). A strict quality control of data recording and checking was conducted to ensure data reliability.

In an effort to provide more consistency in both clinical care and research of patients with MetSyn, we here used the frequently adopted 'harmonised' definition of MetSyn in the joint statement by the IDF, NIH, AHA, International Atherosclerosis Society, World Heart Federation and the International Association for the Study of Obesity in 2009.[3] Three abnormal findings out of five components would qualify a person for the MetSyn. The cut-off points were uniformly defined for all components except WC, for which national or regional cut-off points can be used.

Statistical analyses

Baseline characteristics of cases and controls were expressed as medians (IQRs) or proportions. Differences between the two groups were determined by the t-test/Wilcoxon tests for continuous variables depending on data distribution and by the X^2 tests for categorical variables.

To evaluate the association of MetSyn and its components in individual and in combination with cancer risk, conditional logistic regression was used to compute ORs and 95% CIs. Both univariate model and multivariate model were used. The multivariate model was first adjusted for education level, smoking status, drinking status and depression scores and then adjusted additionally for marital status. In sensitivity analysis, we used the IPTW (inverse probability of treatment weighting) to check the stability of the results. Restricted cubic splines were used to examine the association of individual MetSyn components with cancer risk assuming linear and non-linear distribution. In order to avoid reverse causality, a sensitivity analysis was conducted, in which cancer cases that occurred in the first 2 years of follow-up (survey at 2013) were excluded.

All analyses were performed using the SAS statistical package V.9.4 (SAS Institute). All p values were based on two-sided tests, with the statistical significance level set to 0.05.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Table 1 presents the demographic characteristics, socioeconomic status, psychosocial activity, health behaviours and the biochemical indexes at baseline for the 306 patients with incident cancer identified during the follow-ups and their 918 concurrent cancer-free controls. There was no statistically significant difference between cases and controls according to these variables. Women slightly outnumbered men for both cases and controls. A bit more people were living in rural areas. Two-thirds of participants had the highest achievement of education of primary school or even lower. Participants who were single accounted for 10% of all. In addition, over one-fifth of subjects had a history of smoking or drinking.

In table 2, we observed that significantly elevated cancer risk was associated with MetSyn when the number of MetSyn components was over three (OR: 1.88; 95% CI: 1.19 to 2.97), or when components contained any of elevated TG (OR: 1.61; 95% CI: 1.05 to 2.48), reduced HDL-C (OR: 2.33; 95% CI: 1.40 to 3.86) or elevated BP (OR: 1.65; 95% CI: 1.04 to 2.59) before multiple adjustments. However, any unique MetSyn component was not found to be associated with increased cancer incidence. Also, under either linear or non-linear assumption, we did not observe significant association between unique MetSyn component and cancer risk after multiple-adjusted restricted cubic splines (figure 2).

As shown in table 3, we investigated how the MetSyn components in unique or joint ways impacted the risk of incident cancer after multiple adjustments in various models. Similar results were consistently observed in model 1, model 2 and IPTW model except for non-significance of the OR of elevated TG as a unique MetSyn component in the IPTW model. In order to avoid reverse causality, a sensitivity analysis was conducted, in which cancer cases that occurred in the first 2 years of follow-up were excluded. Compared with reference having no MetSyn components, MetSyn was still associated with increased cancer risk.

We further aimed to explore the association by types of cancer. Confined to the limited number of incident cancer cases, we performed stratified analyses according to which system cancer belonged to (table 4). We found the highest association between MetSyn components and

Table 1 Characteristics of cancer cases and matched controls

Characteristics	Controls (N=918)	Cases (N=306)	P value
Demographic characteristics			
Age (years)*	58 (52–64)	58 (52–64)	–
Sex*			–
Male	360 (40.0)	120 (40.0)	
Female	540 (60.0)	180 (60.0)	
Living place			0.738
Urban	377 (41.1)	129 (42.2)	
Rural	541 (58.9)	177 (57.8)	
Socioeconomic status			
Education			0.864
Below primary school	454 (49.5)	144 (47.1)	
Primary school	187 (20.4)	68 (22.2)	
Middle school	181 (19.6)	60 (19.6)	
High school and above	96 (10.5)	34 (11.1)	
Income	21 000 (4320–44 850)	19 463 (4320–47 801)	0.936
Psychosocial activity			
CESD (Center for Epidemiologic Studies Depression) score	7.0 (3.9–13.0)	8.0 (4.0–13.2)	0.136
Social activities	443 (48.3)	137 (44.8)	0.29
Marital status			0.794
Partnered	814 (88.7)	273 (89.2)	
Single	104 (11.3)	33 (10.8)	
Cognitive score	14 (10–17)	14 (10–17)	0.491
Health behaviours			
Smoking	247 (26.9)	91 (29.7)	0.337
Drinking	194 (21.1)	65 (21.2)	0.968
Sleep duration	6.0 (5–8)	6.0 (5–7.5)	0.103
Biochemical indexes			
hsCRP (mg/L)	1.9 (0.7–5.7)	1.9 (0.7–5.7)	0.237
Glycosylated haemoglobin (%)	5.2 (4.9–5.5)	5.2 (4.8–5.5)	0.716
Total cholesterol (mg/dL)	192.5 (167.4–217.0)	193.7 (167.0–214.9)	0.917
HDL-C (mg/dL)	49.5 (40.6–59.9)	48.3 (38.2–59.9)	0.31
LDL-C (mg/dL)	115.2 (93.6–139.2)	114.0 (92.7–136.5)	0.395
Triglycerides (mg/dL)	108.9 (76.1–167.3)	112.0 (75.6–174.3)	0.61
Glucose (mg/dL)	102.6 (93.6–117.0)	104.9 (93.6–120.8)	0.205
Blood urea nitrogen (mg/dL)	15.2 (12.4–18.3)	15.6 (12.9–18.7)	0.129
Creatinine (mg/dL)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.25
Uric acid (mg/dL)	4.3 (3.6–5.2)	4.4 (3.6–5.3)	0.283
Cystatin C (mg/dL)	1.0 (0.8–1.1)	1.0 (0.8–1.1)	0.342

Data presented as frequency (%) or median (IQR).
*Represents the matching variable.
†
HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol.

female reproductive system and breast cancer (OR: 4.22; 95% CI: 1.62 to 10.95). Digestive system cancer was also significantly associated with MetSyn components (OR: 1.67; 95% CI: 1.11 to 2.53).

The two-way joint effects of MetSyn components on the risk of cancer were listed in table 4. A series of elevated cancer risk over twofold was widely observed for the combined components of MetSyn, including elevated TG

Table 2 Association between components of MetSyn and cancer incidence based on univariate analysis

			Univariate analysis	
	Controls (N=918)	Cases (N=306)	OR (95% CI)	P value
No MetSyn component	138	36	1 (ref)	
Any MetSyn components	780	270		
No of components of MetSyn				
1	303 (38.9)	93 (34.5)	1.19 (0.76 to 1.86)	0.442
2	253 (32.4)	74 (27.4)	1.16 (0.73 to 1.84)	0.542
≥3	224 (28.7)	103 (38.1)	1.88 (1.19 to 2.97)	0.007
P for trend				0.006
Unique MetSyn component				
Elevated waist circumference	84 (27.7)	28 (30.1)	2.10 (0.77 to 5.73)	0.148
Elevated triglycerides	34 (11.2)	11 (11.8)	1.49 (0.58 to 3.80)	0.410
Reduced HDL cholesterol	0	0		
Elevated blood pressure	33 (10.9)	12 (12.9)	1.10 (0.45 to 2.69)	0.833
Elevated fasting plasma glucose	152 (50.2)	42 (45.2)	1.04 (0.57 to 1.89)	0.907
Any MetSyn components				
Elevated waist circumference	399 (51.2)	142 (52.6)	1.50 (0.93 to 2.43)	0.098
Elevated triglycerides	319 (40.9)	132 (48.9)	1.61 (1.05 to 2.48)	0.030
Reduced HDL cholesterol	91 (11.7)	55 (20.4)	2.33 (1.40 to 3.86)	0.001
Elevated blood pressure	217 (27.8)	91 (33.7)	1.65 (1.04 to 2.59)	0.032
Elevated fasting plasma glucose	538 (69.0)	190 (70.4)	1.37 (0.91 to 2.07)	0.131

HDL, high-density lipoprotein; MetSyn, metabolic syndrome.

and reduced HDL, reduced HDL and obesity, reduced HDL and increased BP, reduced HDL and increased FPG before and after multiple adjustments. Very interestingly, reduced HDL-C, as a unique MetSyn component, was not observed among any study participant in the present study (table 2). However, we found that reduced HDL seemed to play an important role in secondary cancer risk only when it was together with other MetSyn components (table 5).

DISCUSSION

We conducted a nested case–control study based on the prospective CHARLS cohort study which included a large representative sample of the general population in China, 17 708 individuals in 10 257 households at baseline. It is the first of its kind to examine the association of MetSyn unique component and its combination at a nationally representative population aged ≥45 years old with cancer

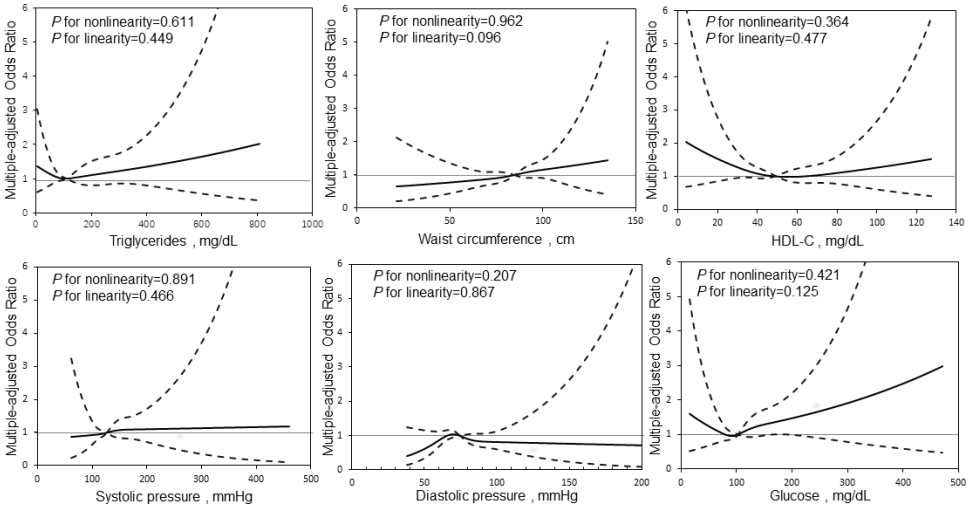

Figure 2 Association of unique MetSyn component with cancer incidence assuming linear or non-linear relationship. HDL-C, high-density lipoprotein cholesterol; MetSyn, metabolic syndrome.

Table 3 Associations of MetSyn and its components with the incidence of cancer in different models

			Model 1		Model 2		IPTW	
	Controls (918)	Cases (306)	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
No MetSyn component	138	36	1 (ref)		1 (ref)		1 (ref)	
Any MetSyn components	780	270						
No of components of MetSyn								
1	303 (38.9)	93 (34.5)	1.21 (0.77 to 1.89)	0.408	1.21 (0.77 to 1.88)	0.387	1.03 (0.85 to 1.24)	0.798
2	253 (32.4)	74 (27.4)	1.20 (0.75 to 1.91)	0.448	1.20 (0.75 to 1.91)	0.452	1.01 (0.82 to 1.24)	0.931
≥3	224 (28.7)	103 (38.1)	1.96 (1.23 to 3.11)	0.005	1.95 (1.23 to 3.10)	0.005	1.65 (1.06 to 2.58)	0.026
P for trend				0.006		0.003		0.302
Unique MetSyn component								
Elevated waist circumference	84 (27.7)	28 (30.1)	2.09 (0.75 to 5.81)	0.157	2.06 (0.74 to 5.77)	0.169	1.10 (0.80 to 1.51)	0.577
Elevated triglycerides	34 (11.2)	11 (11.8)	1.43 (0.54 to 3.74)	0.472	1.45 (0.55 to 3.83)	0.451	1.15 (0.84 to 1.57)	0.390
Reduced HDL cholesterol	0	0	–	–				
Elevated blood pressure	33 (10.9)	12 (12.9)	1.07 (0.43 to 2.68)	0.881	1.05 (0.42 to 2.63)	0.924	1.30 (0.95 to 1.79)	0.106
Elevated fasting plasma glucose	152 (50.2)	42 (45.2)	1.05 (0.57 to 1.94)	0.877	1.08 (0.58 to 2.01)	0.800	0.90 (0.73 to 1.11)	0.333
Any MetSyn components								
Elevated waist circumference	399 (51.2)	142 (52.6)	1.54 (0.95 to 2.51)	0.080	1.54 (0.95 to 2.50)	0.083	1.02 (0.81 to 1.28)	0.854
Elevated triglycerides	319 (40.9)	132 (48.9)	1.66 (1.07 to 2.56)	0.022	1.65 (1.07 to 2.56)	0.023	1.01 (0.82 to 1.25)	0.924
Reduced HDL cholesterol	91 (11.7)	55 (20.4)	2.40 (1.44 to 4.01)	<0.001	2.40 (1.44 to 4.01)	<0.001	1.56 (1.02 to 2.40)	0.041
Elevated blood pressure	217 (27.8)	91 (33.7)	1.69 (1.07 to 2.67)	0.024	1.69 (1.07 to 2.67)	0.025	1.28 (1.03 to 1.60)	0.029
Elevated fasting plasma glucose	538 (69.0)	190 (70.4)	1.42 (0.93 to 2.15)	0.101	1.41 (0.93 to 2.14)	0.105	0.96 (0.80 to 1.15)	0.636
No of components of MetSyn*								
0	110	31	1 (ref)		1 (ref)		1 (ref)	
1	267	76	1.04 (0.64 to 1.69)	0.876	1.04 (0.64 to 1.69)	0.869	0.91 (0.74 to 1.12)	0.358
2	210	64	1.15 (0.69 to 1.89)	0.597	1.15 (0.69 to 1.90)	0.593	0.95 (0.76 to 1.20)	0.683
≥3	202	92	1.78 (1.09 to 2.93)	0.022	1.79 (1.09 to 2.94)	0.022	1.60 (1.00 to 2.56)	0.050

Model 1: adjusted for education level, smoking status, drinking status and depression scores.
Model 2: model 1 with marital status.
IPTW: adjusted for age, sex, education level, smoking status, drinking status and depression scores.
*The first visit at 2013 was excluded.
HDL, high-density lipoprotein; IPTW, inverse probability of treatment weighting; MetSyn, metabolic syndrome.

Table 4 The stratified analyses according to systems that cancer belonged to

Types of cancer	Cases	Controls	OR (95% CI)	P value
Cancer of the digestive system (oral cavity, oesophagus, stomach, colon or rectum, liver, pancreas)	76	228	1.67 (1.11 to 2.53)	0.015
Respiratory cancer (lung, larynx, other pharynx)	46	138	1.10 (0.47 to 2.60)	0.825
Cancers of the female reproductive system and breast cancer (ovary, cervix, endometrium)	77	231	4.22 (1.62 to 10.95)	0.003
Others	107	321	1.70 (0.85 to 3.39)	0.132

risk. We observed elevation in cancer risk associated with MetSyn in a significant way when the number of MetSyn components was over three that could be any of the five factors, or when components contained any of elevated TG, reduced HDL-C, or elevated BP before and after multiple adjustments. To avoid reversed association, we performed a sensitivity analysis exclusive of first wave of survey at 2013, generating the consistent results. The strongest association was among female reproductive system and breast cancer. Notably, any unique MetSyn component was not found to be associated with increased cancer incidence. Very interestingly, we found that reduced HDL played an important role in secondary cancer risk when it was together with other MetSyn components while it, as a unique MetSyn component, was not observed among any study participant in this study.

The present study has a number of strengths. First, our study is the first one of its kind in Asia that was based on a national representative population aged over 45 years old, with good generalisability among these populations. Second, a strict quality control of data recording and checking was conducted to ensure data reliability. Third, a series of covariables was collected so that multiple adjustments became available. Fourth, a sensitivity analysis was conducted to avoid reverse causality. Fifth, several multiple models were used to ensure the replicability of the results. In addition, we assumed the 'harmonised' definition of MetSyn, which was verified to fit our research purpose well. However, limitations still exist for this study, especially those related to methodology. First, relatively short period of follow-up limited our ability to identify more cancer cases, which could have hindered the statistical power for the stratified analyses by the sites of cancer. Second, the incident cancer cases were identified by self-reporting, thus asynchronous occurrence of MetSyn and cancer still could not be totally excluded because of self-report, although we had reduced the chance as far as possible by setting a strict time point for participants to answer their diagnosis during the follow-up. Additionally, generalisability of our study results with respect to non-Asian populations may be hindered.

Our findings that 1.88-fold increased cancer risk was observed after MetSyn (≥3 components) and any unique MetSyn component was not found to be associated with increased cancer incidence together may suggest that MetSyn should be treated as an integrated medical condition rather than its parts as for its impact on the onset of incident cancer, which strengthens the applicability of 'harmonised' definition of MetSyn in clinical treatment and management. MetSyn has been documented to be correlated with a number of cancers.[5 15–18] Biological links between MetSyn and cancer risk had involved as many as factors and signalling pathways described in deregulation of cytokine production, chronic inflammatory state, insulin-like growth factor system, and hormones and proinflammatory cytokines.[6 15] We speculated that the possible underlying mechanisms for reduced HDL to play an important role in secondary cancer risk may be that HDL could impact the level of cholesterol which plays a crucial role in cancer progression by enhancing cell proliferation, migration and invasion, especially for endocrine-related cancer. The cluster of metabolic components over three or more that conferred an increased risk of cancer caused to reflect the underlying mechanism which could be partially the worse inflammatory state, disturbed metabolism or the combined action of these mechanisms. All of these warrant further study to explore.

Although there are a number of studies having documented the association of MetSyn with risk of cancer, the different definitions of MetSyn and components make it difficult to compare their results. Some of them had already reported association between MetSyn and its components with cancer risk.[19–25] Although contradicting results widely existed, our finding of null association between unique MetSyn component and risk of cancer was consistent with results from some large studies and merited attention. Based on a cohort of 220 622 men free of prostate cancer (PCa) diagnosis from the UK Biobank, Monroy-Iglesias *et al*[20] used the measurements of MetSyn including HDL-C, BP, TG, glycosylated haemoglobin and WC at baseline, to explore the association of MetSyn components with the risk of PCa.[20] A total of 5409 men in the study developed PCa during a median follow-up of 6.9 years. There were no associations found with PCa risk and individual measurements of TG, HDL, BP or WC. In EPIC Study, negative association was observed for most individual MetSyn components and breast cancer.[26] A total of 22 494 women recruited during 1993–1998 from four EPIC Study centres in Italy was followed up for up to 15 years in a case–cohort study. They observed significantly increased breast cancer risk among women with diagnosis of MetSyn (HR: 1.52, 95% CI: 1.14 to 2.02). However, elevated blood glucose was the only component of MetSyn which was significantly associated with

Table 5 The combined effect of components of MetSyn on cancer incidence

				Univariate analysis		Multivariate analysis	
	Variable		Cases/Controls	OR (95% CI)	P value	OR (95% CI)	P value
Triglycerides	TG	Waist circumference					
	(-)	(-)	105/468	one ref		one ref	
	(+)	(-)	59/215	1.31 (0.90,1.90)	0.16	1.30 (0.89,1.89)	0.173
	(-)	(+)	69/305	1.13 (0.73,1.75)	0.582	1.10 (0.76,1.61)	0.617
	(+)	(+)	73/236	1.71 (1.10,2.65)	0.016	1.63 (1.11,2.40)	0.012
	TG	HDL					
	(-)	(-)	174/773	one ref		one ref	
	(+)	(-)	77/305	1.17 (0.86,1.59)	0.334	1.16 (0.85,1.58)	0.357
	(-)	(+)	0	–		–	
	(+)	(+)	55/146	2.05 (1.41,2.98)	<0.001	2.04 (1.39,2.99)	<0.001
	TG	Blood pressure					
	(-)	(-)	132/603	one ref		one ref	
	(+)	(-)	83/313	1.28 (0.93,1.76)	0.126	1.28 (0.93,1.76)	0.129
	(-)	(+)	42/170	1.17 (0.78,1.76)	0.438	1.14 (0.77,1.71)	0.517
	(+)	(+)	49/138	1.97 (1.32,2.95)	<0.001	1.89 (1.26,2.86)	0.002
	TG	Fasting plasma glucose					
	(-)	(-)	82/357	one ref		one ref	
	(+)	(-)	34/139	1.09 (0.69,1.72)	0.722	1.30 (0.89,1.89)	0.173
	(-)	(+)	92/416	0.95 (0.68,1.75)	0.76	1.10 (0.76,1.61)	0.617
	(+)	(+)	98/312	1.54 (1.09,2.17)	0.015	1.63 (1.11,2.40)	0.012
HDL	HDL	Waist circumference					
	(-)	(-)	139/614	one ref		one ref	
	(+)	(-)	25/69	1.94 (1.14,3.30)	0.015	1.99 (1.16,3.40)	0.012
	(-)	(+)	112/464	1.24 (0.84,1.84)	0.285	1.20 (0.87,1.67)	0.271
	(+)	(+)	30/77	2.42 (1.38,4.26)	0.002	2.27 (1.35,3.84)	0.002
	HDL	Blood pressure					
	(-)	(-)	183/827	one ref		one ref	
	(+)	(-)	32/89	1.96 (1.24,3.10)	0.003	1.99 (1.25,3.19)	0.004
	(-)	(+)	68/251	1.34 (0.96,1.87)	0.087	1.28 (0.93,1.78)	0.136
	(+)	(+)	23/57	2.40 (1.37,4.20)	<0.001	2.22 (1.26,3.92)	0.006
	HDL	Fasting plasma glucose					
	(-)	(-)		one ref		one ref	
	(+)	(-)	103/453	1.47 (0.74,2.91)	0.275	1.45 (0.72,2.90)	0.295
	(-)	(+)	13/43	1.05 (0.79,1.39)	0.755	1.07 (0.80,1.43)	0.63
	(+)	(+)	148/625	2.26 (1.45,3.52)	<0.001	2.33 (1.47,3.68)	<0.001
Blood pressure	BP	Waist circumference					
	(-)	(-)	117/525	one ref		one ref	
	(+)	(-)	47/158	1.49 (0.99,2.26)	0.057	1.44 (0.96,2.15)	0.077
	(-)	(+)	98/391	1.28 (0.86,1.93)	0.219	1.27 (0.90,1.80)	0.171
	(+)	(+)	44/150	1.61 (0.99,2.62)	0.057	1.52 (0.97,2.36)	0.066
	BP	Fasting plasma glucose					
	(-)	(-)	92/396	one ref		one ref	
	(+)	(-)	24/100	1.05 (0.62,1.78)	0.861	1.01 (0.60,1.69)	0.984
	(-)	(+)	123/520	1.02 (0.75,1.39)	0.892	1.04 (0.76,1.42)	0.797
	(+)	(+)	67/208	1.59 (1.09,2.32)	0.016	1.54 (1.01,2.25)	0.026

Adjusted for education level, smoking status, drinking status, depression scores and marital status.
HDL, high-density lipoprotein; MetSyn, metabolic syndrome.

breast cancer risk in all women (HR: 1.47, 95% CI: 1.13 to 1.91) and postmenopausal women (HR: 1.89, 95% CI: 1.29 to 2.77). Results from another EPIC-based study[27] found that plasma total cholesterol, low-density lipoprotein cholesterol and TG were not significantly related to overall cancer risk. However, the presence of MetSyn was associated with cancer risk (RR(Relative Risk): 2.12; 95% CI: 1.51 to 2.97), which increased with the number of MetSyn components (p(trend)=0.02).

Our findings affirmed that MetSyn components may act synergistically to increase cancer risk. That more components (≥3) of MetSyn were related to a higher risk of cancer observed in our study was supported by findings from another study where OR for three versus null factors was 2.57 (95% CI: 1.20 to 5.52; p(trend)=0.0021), as compared with a 30%–70% increased risk for the factors in single.[28] Our finding was supported by another study[29] conducted in Asia, in which a total of 930 055 postmenopausal women aged 40–74 years were examined in the National Health Screening Programme in 2009–2010 and 2011–2012. Our finding that the risk of breast cancer increased as the number of the components increased (HR: 1.46, 95% CI: 1.26 to 1.61 for women with all five components) was inconsistent with the results based on SEER Database. In this case–control design using the SEER Database, authors investigated the relationship between endometrial cancer risk and the MetSyn components independently or in combination.[30] They found that elevated risk of endometrial cancer was not only observed among patients with MetSyn (OR: 1.39; 95% CI: 1.32 to 1.47) but also those with its individual components including high BP (OR: 1.31; 95% CI: 1.25 to 1.36), high TG (OR: 1.13; 95% CI: 1.08 to 1.18), impaired fasting glucose (OR: 1.36; 95% CI: 1.30 to 1.43) and overweight (OR: 1.95; 95% CI: 1.80 to 2.11). However, we did not perform association of MetSyn with subsequent endometrial cancer risk confined to a limited number of cases after stratification. Another PCa study based on North America data[31] found that a history of MetSyn (≥ 3 vs <3 components) was associated with a reduced risk of PCa (OR: 0.70; 95% CI: 0.60 to 0.82) after considering potential confounders among people at a young age (≤40 years) at MetSyn onset. A decrease in risk was observed with the number of MetSyn components, suggesting a synergistic interaction of the components.

Stratified analyses in our study showed that increased cancer risk was observed in digestive organ (OR: 1.67; 95% CI: 1.11 to 2.53) as well as female reproductive system and breast cancer (OR: 4.22; 95% CI: 1.62 to 10.95). Authors analysed data from a case–control study[32] which included 454 incident endometrial cancer cases and 798 controls admitted to the same hospitals. They found that the enhanced risk of endometrial cancer was related to type 2 diabetes (OR: 2.18), hyperlipidaemia (OR: 1.20), hypertension (OR: 1.77), body mass index >30 kg/m^2 (OR: 3.83) and various definitions of central obesity (OR: 1.62–2.23), which was in line with our findings regarding female reproductive system and MetSyn. Conflicting results were reported using data from the health information system of the cancer registry.[18] Overall, in 16 677 subjects identified in 45 828 person-years, 823 incident cancers occurred. Significantly, increased risks of pancreatic cancer in men (SIR(Standardized Incidence Ratio) 178 (114–266)) and colorectal cancer in women (SIR 133 (101–170)) were also observed. Non-significant increased risks were also observed in women for liver, gall bladder and biliary tract, breast and endometrial cancers.

In the joint analyses, we observed a widely elevated cancer risk of over twofold secondary to reduced HDL only when together with other MetSyn components. However, reduced HDL, as a unique MetSyn component, was not observed among any of our study participants. The reversed association of HDL with risk of cancer had been reported in epidemiological studies.[33–36] Our study further revealed that reduced HDL may play its role in cancer risk by its synergistic effect on other MetSyn components, which warrants further investigation when more data were available in CHARLS.

To sum up, this is one of the first studies examining whether previous diagnosis of MetSyn, unique or joint components, will impact subsequent cancer risk, where our results suggest that MetSyn should be better treated as an integrated medical condition with its components collaboratively for the cancer management and therapy. Further, not only obesity but even subtle metabolic disturbances may give rise to cancer. Prevention of MetSyn through lifestyle changes could confer protection against cancer.

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