

The Effect of Metabolic Syndrome on Head and Neck Cancer Incidence Risk: A Population-based Prospective Cohort Study

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Research

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Abstract

Background

There are limited evidences clarifying the impact of metabolic syndrome (MS) and its components on head and neck cancer (HNC) incidence risk. We explored the correlation between MS, MS components, and the combined effects of MS and C-reactive protein (CRP) and HNC risk.

Methods

This is a prospective analysis of 474,929 participants from the UK Biobank cohort. Cox proportional hazard regression was utilized to assess the hazard ratio (HR) and 95% confidence interval (CI), and to explore the non-linear correlation between an individual MS component and HNC risk.

Results

Individuals with MS (HR, 1.05; 95%CI, 0.90-1.22) had no higher risk of HNC than those without MS and those with more MS components showed no higher HNC risk. Nevertheless, we observed that MS component hyperglycaemia (HR, 1.22; 95%CI, 1.02-1.45) was independently correlated with elevated HNC risk. In a non-linear manner, waist circumference and high-density lipoprotein (HDL) showed a U-shape association with HNC risk. Further linear analysis indicated that male waist circumference, female waist circumference (when ≥ 93.16 cm), male HDL (when ≥ 1.45 mmo/L) and blood glucose were positively correlated with HNC risk. Increased CRP (≥ 1.00 mg/dL) elevated HNC risk and individuals with MS and CRP ≥ 1.00 mg/dL had the highest HNC risk (HR, 1.29; 95%CI, 1.05-1.58).

Conclusions

Although MS are not correlated with elevated HNC risk, high male waist circumference, high female waist circumference (≥ 93.16 cm), high male HDL (≥ 1.45 mmo/L) and high blood glucose are independent risk factors of HNC. We also recommended a potential combined effect of MS and CRP in head and neck tumorigenesis.

Introduction

Head and neck cancer (HNC) constituted of 5% of all tumors¹. Approximately 500,000 individuals are diagnosed each year, of which 350,000 cases die^{2,3}. Sixty percent of patients are already in advanced stage when being diagnosed^{4,5}. Although treatments including surgery, radiotherapy, and chemotherapy have been widely used, the 5-year survival rate of HNC is still only 50%, and the local recurrence rate is up to 50%, and the distant metastasis rate is 25%^{6,7}. Even if the treatment is successful, the patients may cause mental illness due to impaired vocalization, chewing, swallowing, respiratory function, and facial changes induced by surgery or radiotherapy. Studies have shown that among all HNC components, the suicide rate of patients with oral oropharyngeal cancer (53.1/100,000) and laryngeal cancer

(46.8/100,000) second only to lung cancer (81.7/100,000) and stomach cancer (71.7/100,000), ranking third and fourth respectively⁸. Therefore, early identification of risk factors is essential to reduce the morbidity and mortality of HNC.

Metabolic syndrome (MS) is a group of metabolic abnormalities, including hypertension, central obesity, elevated triglyceride, low high-density lipoprotein (HDL) cholesterol, and insulin resistance⁹. MS or its components are strongly correlated with cancer incidence risk and mortality. It has shown to increase the incidence of liver^{10,11}, colorectal¹²⁻¹⁴, pancreatic¹⁵, endometrial¹⁶ and breast cancer^{17,18}. MS component diabetes mellitus is also close associated to cancer risk¹⁹ and abdominal obesity is notably correlated with higher risk and mortality of most common cancers²⁰. The mechanism by which MS may influence cancer development is similar. The possible mechanisms of MS carcinogenesis are as follows: (1) hyperinsulinemia and insulin resistance, (2) chronic subclinical inflammation, (3) abnormal sex hormone metabolism, (4) injury induced by exposure of endocrine disruptors and air pollution, (5) Chronic hyperglycemia and (6) Circadian rhythm disorder²¹. To our best knowledge, there is only one investigation showing inverse relations between MS and type 2 diabetes and HNC. However, to date, there have been no studies based on prospective analysis to explore the correlation between MS and HNC risk.

UK Biobank recruited more than 500 thousand participants with an age from 37 to 73 year-old recruited in United Kingdom from year 2006 to 2010. UK Biobank documented beyond 2,000 features, such as anthropometric measurements, sociodemographic assessments, clinical diagnosis and self-reported behavioral outcomes, which provides us with a new chance to assess risk factors of cancer development in a large population-based samples. Based on the UK Biobank dataset, this study tried to clarify the major MS components connected to HNC; to explore possible non-linear correlations between its components and HNC; and to detect the mutual relations amongst MS, C-reactive protein (CRP), and HNC risk.

Materials And Methods

Study design and participants

Our data application was approved by UK Biobank on August 2019 and the application number was 51671. Detailed information on the research design and data collection methods of UK Biobank cohort have been published²³. We included all UK Biobank participants who reported data on any measure of the MS components. The participants with any cancers being diagnosed before (n = 26868) were excluded (apart from non-melanoma skin cancer with a code of ICD-10 C44). For gestation will increase waist circumference and lead to potential metabolic changes, pregnant women (n = 149) were also excluded. The participants were followed until the date of HNC diagnosis or censoring. HNC was identified if participants were diagnosed as any of the following cancers: laryngeal cancer (ICD-10 C32), nasopharyngeal carcinoma (C11), tonsil cancer (C09), oropharyngeal cancer (C10), hypopharyngeal

carcinoma (C12 and C13), nasal cavity and paranasal sinus cancer (C31) and oral cancer (C00-C06). Finally, 474,929 participants were involved in this study.

Ethnic statement

The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee, the England and Wales Patient Information Advisory Group, and the Scottish Community Health Index Advisory Group. All participants provided written informed consent before data collection.

Data collection

Participants were invited to fill out a questionnaire during recruitment in their closest assessment center. Sociodemographic characteristics (i.e., age, gender, ethnicity, education, income levels), lifestyle information (i.e., physical activity, tobacco smoking, alcohol drinking), complications (i.e., diabetes mellitus, hypertension) and medicine intake information were collected. The International Physical Activity Questionnaire and the food frequency questionnaire were utilized to evaluate physical activity and diet intake respectively, which has been verified in a previous study²⁴. Right arm diastolic and systolic blood pressure (DBP and SBP) was measured twice using an electronic sphygmomanometer and the average value was used. After normal exhalation, a Wessex non-stretchable spring tape measure was utilized to measure the waist circumference (cm) at the level of the umbilicus twice²⁵. Plasma concentration of HDL cholesterol, glucose and triglycerides were tested utilizing a Beckman Coulter AU5800 analyzer. The baseline of CRP concentration was quantified utilizing the immuno-turbidimetric method.

Outcome Assessment

HNC cases were recognized by establishing links with the Health and Social Care Information Centre (located in England and Wales) and the Cancer and Death Registry of the National Health Service Central Register (located in Scotland). For more details about the linking process, please visit <https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=115558>. The person-years were calculated recruitment date to any dates of death, the first HNC, or the end of follow-up (October 30, 2015).

Definition for MS and MS components

We used the definition criteria of MS and its components developed by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)⁹. Individuals with body mass index (BMI) greater than 30 kg/m², or the waist circumference more than the values of cut points that are population- and country-specific definitions was diagnosed as central obesity⁹. Dyslipidaemia for triglycerides (TG) was defined as plasma TG concentration ≥ 1.7 mmol/L (150 mg/dL) or currently on medications for hypertriglyceridemia⁹. HDL cholesterol < 1.0 mmol/L (40 mg/dL) for males and < 1.30 mmol/L (50 mg/dL) for females or specific treatment for previously detected decreased HDL cholesterol was defined as dyslipidaemia for HDL⁹. Hypertension was diagnosed if blood pressure was over 130/85 mmHg, or already receiving antihypertensive treatment⁹. Hyperglycaemia was described as

previously diagnosed type 2 diabetes or fasting plasma glucose ≥ 5.56 mmol/L (100 mg/dL). Participants with 3 or more of 5 risk factors will be diagnosed with metabolic syndrome⁹.

Data Analysis

Cox regression models were utilized to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the correlation of MS and its components with HNC incidence risk. To compare the effect among MS components, we analyzed them as continuous variables to estimate HRs per standard deviation (SD) increase. In addition, we utilized restricted cubic splines for each MS component to explore their potential non-linear correlation with HNC risk. Further, to explore the combined effect between CRP and MS on the influence of HNC risk, we defined 4 risk levels according to MS or CRP levels with a cut-off point of 1.00 mg/dL. And the HRs for HNC risk were calculated when comparing to the No MS plus CRP < 1.00 mg/dL group.

The unadjusted model (model 1) was first conducted. Then we adjusted age and gender in model 2. In model 3, ethnic, education level, index of multiple deprivations, tobacco smoking status, alcohol drinking status, physical activity and portions of fruit and vegetable intake were further adjusted.

$P < 0.05$ with two-tailed was considered as statistical significance. R software (version 3.6.1) was utilized for all statistical analysis.

Results

Among all participants, nearly one-third of them were diagnosed as MS ($n = 140346$, 29.6%). As expected, the participants with MS have higher waist circumference, BMI, blood pressure, the plasma concentration of fasting glucose, TG, and CRP, but lower concentration of HDL cholesterol. MS participants appeared to be older, to have a higher multiple deprivation index, and to have less physical activity. Table 1 showed the baseline characteristics.

Table 1

Baseline characteristics of participants according to MS in the UK biobank cohort.

Metabolic syndrome (N)	No (n = 334583)	Yes (n = 140346)
Average follow-up years, Mean (SD)	6.58 (1.23)	6.49 (1.30)
Age at participation, Mean (SD)	55.5 (8.15)	58.3 (7.64)
BMI, Mean (SD), kg/m ²	25.9 (3.86)	31.0 (4.90)
Waist circumference, Mean (SD), cm	85.8 (11.3)	101 (12.1)
HDL cholesterol, Mean (SD), mmol/L	1.55 (0.366)	1.22 (0.303)
Triglycerides, Mean (SD), mmol/L	1.44 (0.777)	2.42 (1.19)
Fasting glucose, Mean (SD), mmol/L	4.88 (0.671)	5.63 (1.87)
SBP, Mean (SD), mm Hg	137 (19.7)	146 (17.9)
DBP, Mean (SD), mm Hg	80.9 (10.6)	85.4 (10.3)
Primary site of cancer, N		
Larynx	61	42
Tonsil	92	42
Oral cavity	181	111
Nasal cavity and sinuses	16	6
Oropharynx	14	7
Hypopharynx	20	4
Others	111	99
Gender, N (%)		
Female	188906 (56.5%)	66956 (47.7%)
Male	145677 (43.5%)	73390 (52.3%)
Education level, N (%)		
College or University degree	117845 (35.2%)	35265 (25.1%)
Other	162865 (48.7%)	70220 (50.0%)
unknown/missing	53873 (16.1%)	34861 (24.8%)
Ethnicity, N (%)		
Non-White	315381 (94.3%)	131082 (93.4%)

Metabolic syndrome (N)	No (n = 334583)	Yes (n = 140346)
white	17645 (5.3%)	8492 (6.1%)
unkonwn/missing	1557 (0.5%)	772 (0.6%)
Index of multiple deprivation quintile, N (%)		
1th	61047 (18.2%)	20643 (14.7%)
2th	59990 (17.9%)	21823 (15.5%)
3th	58520 (17.5%)	23158 (16.5%)
4th	56301 (16.8%)	25571 (18.2%)
5th	52601 (15.7%)	29330 (20.9%)
missing	46124 (13.8%)	19821 (14.1%)
Smoking status, N (%)		
Current	34587 (10.3%)	15915 (11.3%)
Previous	107678 (32.2%)	54704 (39.0%)
Never	190793 (57.0%)	68809 (49.0%)
unkonwn/missing	1525 (0.5%)	918 (0.7%)
Alcohol consumption, N (%)		
Daily or almost daily	72332 (21.6%)	23976 (17.1%)
1–4 times a week	169384 (50.6%)	62723 (44.7%)
One to three times a month	35496 (10.6%)	17363 (12.4%)
Special occasions only or never	56642 (16.9%)	35901 (25.6%)
unkonwn/missing	729 (0.2%)	383 (0.3%)
Physical activity, N (%)		
Low	44878 (13.4%)	26981 (19.2%)
Moderate	109466 (32.7%)	45595 (32.5%)
High	117170 (35.0%)	37074 (26.4%)
unkonwn/missing	63069 (18.9%)	30696 (21.9%)
Portions of fruit and vegetable intake, Mean (SD)	4.66 (3.11)	4.52 (3.16)
NSAIDS, N (%)		
No	209520 (62.6%)	67714 (48.2%)

Metabolic syndrome (N)	No (n = 334583)	Yes (n = 140346)
Yes	117629 (35.2%)	70322 (50.1%)
Missing	7434 (2.2%)	2310 (1.6%)
CRP_C, N (%)		
No	145619 (43.5%)	30015 (21.4%)
Yes	161311 (48.2%)	106964 (76.2%)
Missing	27653 (8.3%)	3367 (2.4%)

During an average follow-up of 6.5 years, we recorded 806 HNC cases. Overall, individuals with MS had no significant effect on risk of HNC compared to those without MS (HR, 1.05; 95%CI, 0.90–1.22). More MS components led to higher risk of HNC (3 components: HR, 1.04; 95%CI, 0.88–1.24; 4 components: HR, 1.00; 95%CI, 0.80–1.26; 5 components: HR, 1.30; 95%CI, 0.92–1.84), but no statistical differences were detected. Analysis of MS components reveals that individuals with dyslipidemia for TG (HR, 1.31; 95%CI, 1.31–1.51), hypertension (HR, 1.23; 95%CI, 1.02–1.48) and hyperglycemia (HR, 1.35; 95%CI, 1.14–1.61) had higher hazard for HNC (model 1). After being adjusted by age and gender (model 2), ethnic, education, Index of multiple deprivations, alcohol drinking status, smoking status, fruit and vegetable intake, physical activity, NSAIDS use and CRP (model 3), the association remained noticeably for hyperglycemia (HR, 1.22; 95%CI, 1.02–1.45). See details in Table 2.

Table 2
Risk of head and neck cancer according to MS and its components

	No of cases/ Person-years	Model 1		Model 2		Model 3	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Presence of MS							
No	495/ 2201184	Reference		Reference		Reference	
Yes	311/ 910374	1.27 [1.10, 1.47]	0.001	1.18 [1.02, 1.36]	0.023	1.05[0.90, 1.22]	0.560
No. of MS components							
0-2	483/2167132	Reference		Reference		Reference	
3	191/582520	1.25 [1.06, 1.48]	0.009	1.14[0.96, 1.35]	0.126	1.04[0.88, 1.24]	0.645
4	95/283291	1.26 [1.01, 1.57]	0.043	1.16[0.93, 1.45]	0.187	1.00[0.80, 1.26]	0.978
5	37/78614	1.70 [1.22, 2.38]	0.002	1.58 [1.13, 2.21]	0.008	1.30[0.92, 1.84]	0.132
Center obesity							
No	500/2065978	Reference		Reference		Reference	
Yes	304/1036668	1.10[0.95, 1.26]	0.211	1.19 [1.04, 1.38]	0.015	1.04[0.90, 1.21]	0.592
Dyslipidaemia for TG							
No	141/845849	Reference		Reference		Reference	
Yes	665/2262915	1.31 [1.13, 1.51]	< 0.001	1.06[0.91, 1.23]	0.461	0.95[0.81, 1.10]	0.472
Dyslipidaemia for HDL							
No	301/1501095	Reference		Reference		Reference	

model 1: unadjusted

model 2: Age and gender-stratified model

model 3: additionally adjusted for education, ethnic, Index of multiple deprivation, alcohol consumption, smoking status, physical activity, fruit and vegetable intake, NASIDS use and CRP;

	No of cases/ Person-years	Model 1		Model 2		Model 3	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Yes	464/1438442	1.16[0.98, 1.39]	0.091	1.17[0.98, 1.39]	0.087	1.01[0.84, 1.22]	0.877
Hypertention							
No	528/2095502	Reference		Reference		Reference	
Yes	160/568287	1.23[1.02, 1.48]	0.027	1.02[0.84, 1.22]	0.874	1.00[0.82, 1.20]	0.973
Hyperglycaemia							
No	529/2226708	Reference		Reference		Reference	
Yes	174/459089	1.35[1.14, 1.61]	0.001	1.26[1.06, 1.5]	0.009	1.22[1.02, 1.45]	0.028
model 1: unadjusted							
model 2: Age and gender-stratified model							
model 3: additionally adjusted for education, ethnic, Index of multiple deprivation, alcohol consumption, smoking status, physical activity, fruit and vegetable intake, NASIDS use and CRP;							

When assessing the non-linear effect between individual MS components and HNC incidence risk, we observed a significant U-shape association for waist circumference (Fig. 1A, p-non-linear = 0.004) and HDL (Fig. 1E, p-non-linear = 0.005). Further, we analyzed their association for each gender, which showed that there was no non-linear relation between male waist circumference (Fig. 1B, p-non-linear = 0.394), female HDL (Fig. 1G, p-non-linear = 0.879) and HNC risk. However, a U-shape association between female waist circumference (Fig. 1C, p-non-linear = 0.031), male HDL (Fig. 1F, p-non-linear = 0.005) and HNC risk was observed. No relation was found for TG (Fig. 1D, p-non-linear = 0.098), SBP (Fig. 1H, p-non-linear = 0.849), DBP (Fig. 1I, p-non-linear = 0.258) and blood glucose (Fig. 1J, p-non-linear = 0.075). Based on this results, we divided the female waist circumference and male HDL into two sections with 93.16 cm and 1.45 mmol/L respectively according to the lowest point of U-shape curves to further perform linear analysis.

The linear effect between HNC risk and each MS component was showed in Table 3. Higher male waist circumference was correlated with elevated HNC risk (HR, 1.10; 95%CI, 1.02–1.20). Low female waist circumference (< 93.16 cm) showed no influence on the risk of HNC (HR, 0.92; 95%CI, 0.78–1.08); however, high female waist circumference (\geq 93.16 cm) was positively correlated with HNC risk (HR, 1.47; 95%CI, 1.15–1.89). Interestingly, higher male HDL increased HNC risk (HR, 1.19; 95%CI, 1.04, 1.36) when the concentration was more than 1.45 mmol/L. Male participants had no significant increased risk of HNC (HR, 0.94; 95%CI, 0.85–1.04) when HDL was less than 1.45 mmol/L and there was no correlation

between female HDL with HNC risk (HR, 1.08; 95%CI, 0.92–1.27). Higher blood glucose was correlated with higher HNC risk (HR, 1.06; 95%CI, 1.00-1.12). No relation was found for TG (HR, 0.99; 95%CI, 0.93–1.07), SBP (HR, 1.03; 95%CI, 0.96–1.10) and DBP (HR, 1.00; 95%CI, 0.93–1.08).

Table 3
Risk of head and neck cancer in the UK biobank cohort in relation to MS components

MS components	Model 1		Model 2		Model 3	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Waist circumference (male)	1.19 [1.10, 1.28]	< 0.001	1.19 [1.10, 1.28]	< 0.001	1.10 [1.02,1.20]	0.019
Waist circumference (female)						
<93.16 cm	0.94[0.80, 1.11]	0.469	0.94[0.80, 1.11]	0.471	0.92[0.78, 1.08]	0.311
≥93.16 cm	1.42 [1.11, 1.80]	0.005	1.41 [1.11, 1.80]	0.005	1.47 [1.15, 1.89]	0.003
Triglycerides (mmol/L)	1.12 [1.05, 1.20]	< 0.001	1.03[0.97, 1.11]	0.339	0.97[0.91, 1.04]	0.407
HDL cholesterol (male)						
<1.45 mmol/L	0.88 [0.80, 0.98]	0.014	0.88 [0.80, 0.98]	0.014	0.94[0.85, 1.04]	0.208
≥1.45 mmol/L	1.23 [1.08, 1.40]	0.002	1.23 [1.08, 1.41]	0.001	1.19 [1.04, 1.36]	0.009
HDL cholesterol (female)	1.02[0.87, 1.18]	0.830	1.02[0.88, 1.18]	0.821	1.08[0.92, 1.27]	0.344
Diastolic blood pressure (mmHg)	1.07 [1.00, 1.05]	0.043	0.99[0.92, 1.06]	0.716	0.99[0.93, 1.07]	0.848
Systolic blood pressure (mmHg)	1.09 [1.01, 1.17]	0.018	1.03[0.96, 1.11]	0.415	1.03[0.96, 1.10]	0.451
Blood glucose (mmol/L)	1.09 [1.03, 1.15]	0.002	1.07 [1.01, 1.13]	0.018	1.06 [1.00, 1.12]	0.044
model 1: unadjusted						
model 2: Age and gender-stratified model						
model 3: additionally adjusted for education, ethnic, Index of multiple deprivation, alcohol consumption, smoking status, physical activity, fruit and vegetable intake, NASIDS use and CRP;						

We further explore the relation between HNC incidence risk and CRP, the combined effect of CRP and MS as well. Elevated CRP more than 1.00 mg/dL elevated the risk for HNC (HR, 1.21; 95%CI, 1.02–1.43)

compared to it lower than 1.00 mg/dL (model 3). After evaluating the combined effect of CRP and MS, it was found that both no MS plus elevated CRP (HR, 1.22; 95%CI, 1.02–1.47) and MS plus elevated CRP (HR, 1.29; 95%CI, 1.05–1.58) participants had increased HNC risk compared to those without MS and CRP < 1.00 mg/dL. See details in Table 4.

Table 4

Hazard ratios (HR) with 95% confidence intervals (CI) for head and neck cancer by CRP and joint effect of MS and CRP

	No. of cases / Person- years	Model 1		Model 2		Model 3	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
CRP							
< 1.00 mg/dL	223/1155432	Reference		Reference		Reference	
≥ 1.00 mg/dL	531/1750092	1.39 [1.18, 1.62]	< 0.001	1.44 [1.23, 1.68]	< 0.001	1.21 [1.03, 1.42]	0.021
Joint effect of MS and CRP							
No MS/CRP < 1.00 mg/dL	181/1027524	Reference		Reference		Reference	
No MS/CRP ≥ 1.00 mg/dL	327/1153876	1.42 [1.19, 1.72]	< 0.001	1.45 [1.21, 1.73]	< 0.001	1.22 [1.02, 1.47]	0.033
MS/CRP < 1.00 mg/dL	42/127908	1.50 [1.07, 2.10]	0.018	1.30[0.93, 1.82]	0.126	1.20[0.85, 1.68]	0.298
MS/CRP ≥ 1.00 mg/dL	204/596216	1.58 [1.29, 1.93]	< 0.001	1.61 [1.31, 1.96]	< 0.001	1.29 [1.05, 1.58]	0.017
model 1: Unadjusted							
model 2: Age and gender-stratified model							
model 3: additionally adjusted for education, ethnic, Index of multiple deprivation, alcohol consumption, smoking status, physical activity, fruit and vegetable intake, and NASIDS use;							

Discussion

This is a prospective cohort study involving 474,929 participants and 806 HNC cases. We observed that individuals with MS had no elevated incidence risk of HNC and the risk did not elevate with the amount of MS components. Only hyperglycaemia was independently correlated with HNC risk among all MS components. Linear analysis revealed that male waist circumference, female waist circumference (≥ 93.16 cm), male HDL (≥ 1.45 mmol/L) and blood glucose for each gender were positively correlated with HNC risk. CRP was positively correlated with an elevated incidence risk of HNC, and the risk was elevated in participants with MS, demonstrating MS and CRP had joint effect on the risk of HNC. Our study

comprehensively explored the correlation between MS and HNC risk in the general population and indicated an inflammatory mechanism for HNC development.

To date, there was only one study that exploring the effect of MS on the risk of HNC²². Stott-Miller M et al. suggested a moderate inverse relation between MS and HNC. However, in our study, we observed no association between MS and HNC risk after adjusting several confounders. It is worth noting that Stott-Miller M's study is a retrospective study, but our results is based on a prospective cohort study which have higher evidence level. Inadequate control of key confounding variables, including obesity, smoking time and smoking intensity in Stott-Miller M's study may also lead to the observed reverse association.

Additionally, some researches have assessed the influence of MS on HNC component risk. Zucchetto et al. found no overall association between MS and nasopharyngeal carcinoma, but MS increased the risk of differentiated nasopharyngeal carcinoma²⁷. However, a study conducted in South Korea by Sang-Yeon Kim claimed that MS was an independent risk factor for laryngeal cancer incidence²⁸. Therefore, further analyses concerning the association between MS and HNC subgroups are meaningful in future studies.

In the present study, we observed that one MS component hyperglycaemia was independently associated with increased HNC risk. Hyperglycaemia is considered to be a critical factor in the pathophysiology of MS. Hyperglycaemia, Hyperinsulinemia and insulin resistance are increasing proliferation, angiogenesis, and the destruction of DNA molecules by oxygen-active forms caused by excess glucose, cell migration and apoptosis²⁹⁻³¹. Previous studies suggested that MS elevated the incidence risk of cancer through the change of insulin receptors and activation of growth and transcription factors^{32,33}. Several studies have evaluated the influence of diabetes on HNC risk^{22,34-36}. Stott-Miller M²² suggested that type II diabetes slightly decreased HNC risk. However, the other three studies revealed that diabetes increased HNC risk. Our study observed that blood glucose concentration was an independent risk factor for HNC development. Overweight/obesity is strongly correlated with glucose intolerance and type II diabetes^{37,38}; however, our study observed that central obesity was not an independent risk factor for HNC. Further analysis suggested that waist circumference was significantly correlated with HNC risk in a U-shape manner and higher female waist circumference increased risk when it was more than 93.16 cm, which was consistent with the previous study that suggested moderate-intensity physical activity (equal to short-distance running) may be beneficial for reducing laryngeal cancer risk³⁹. Interestingly, some studies have showed that high level of HDL is protective against cancer; however, we found that high HDL level also increase the risk of HNC in men. HDL levels are higher in patients with epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer. In this part of patients, high HDL levels seem to increase sensitivity to EGFR-tyrosine kinase inhibitors⁴⁰. As well known, more than 70% of HNC have EGFR gene mutations, which may explain why high HDL increase risk of HNC. The concentration of triglycerides, diastolic and systolic blood pressure had no independent influence on HNC risk.

Disorders of the inflammatory condition induced by MS may play an essential role the tumorigenesis. To date, no studies were available in exploring the influence of CRP on HNC risk. In the present study, our

results indicated that CRP, a sensitive biomarker of inflammation in vivo, was independently correlated with an increased HNC incidence risk. Additionally, the HNC risk induced by MS plus CRP was further increased when compared with MS alone or elevated CRP alone. MS individuals had higher blood CRP, regardless of the diverse definition for MS and its components in different studies⁴¹⁻⁴³. This suggested that HNC development in MS individuals may attribute to the inflammatory system disruption. Therefore, it is critical to analyze the combined effects of MS and CRP during early intervention. Further researches are needed to verify these findings.

The primary benefit of this study is that the data are based on a prospective cohort study from the UK biobank, with a verified follow-up time (average 6.5 years) and detailed measurement results. This allows potential confounding factors to adjust the correlation of interest simultaneously. In addition, we investigate the linear and non-linear relationship between all MS components and HNC risk, which has rarely been published in previous studies. Besides, we evaluated the interaction of MS and CRP with HNC, which may provide a pathological basis for MS tumorigenesis.

This study still has some limitations. First, as an observational study, although we have used complementary analytical methods to assess its epidemiological relationship steadily, we cannot assess the exact causal relationship between MS and HNC development. Second, because the MS component has only been measured once, it is impossible to assess these risk factors' impact over time. Finally, due to the absence of histological information, it was limited to analyze the effects of MS on the HNC subtype.

In conclusion, this study suggested no correlation between MS and HNC risk. However, high male waist circumference, high female waist circumference (≥ 93.16 cm), high male HDL (≥ 1.45 mmol/L) and high blood glucose are independently elevated the risk of HNC. We also indicated a combined effect of MS and CRP in HNC tumorigenesis, which may bring us new perception to study the pathological changes of HNC development.

Declarations

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Authors' Contributions:

Conception and design: Huaili Jiang, Jinqiu Yuan and Xinsheng Huang.

Development of methodology: Huaili Jiang and Qiangsheng He.

Acquisition of data: Huaili Jiang, Lei Zhou.

Data analysis and explanation (e.g., computational analysis, statistical analysis, biostatistics): Huaili Jiang and Qiangsheng He.

Figure and table preparing: Huaili Jiang and Kanglun Jiang

Writing and revision of the manuscript: Huaili Jiang and Kanglun Jiang.

Study supervision: Jinqiu Yuan and Xinsheng Huang.

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Conflicts of Interest Statement

There are no potential conflicts of interest to declare.

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Figures

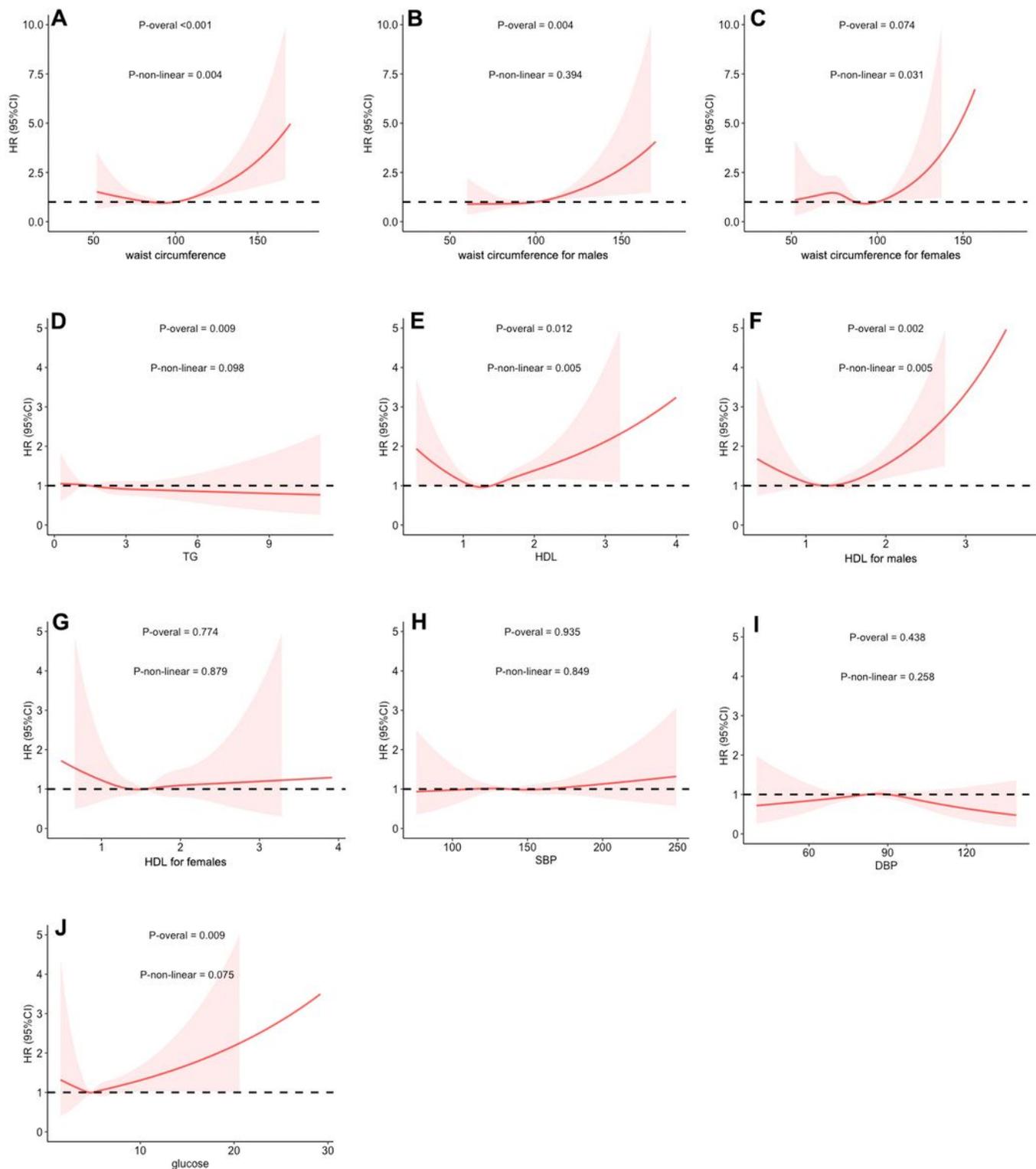


Figure 1

The non-linear effect between individual MetS components and HNC risk. A, waist circumference; B, waist circumference for males. C, waist circumference for females. D, TG (Triglyceride); E, HDL (high-density lipoprotein); F, HDL for males; G, HDL for females. H, SBP (systolic blood pressure); I, DBP (diastolic blood pressure); J, blood glucose.

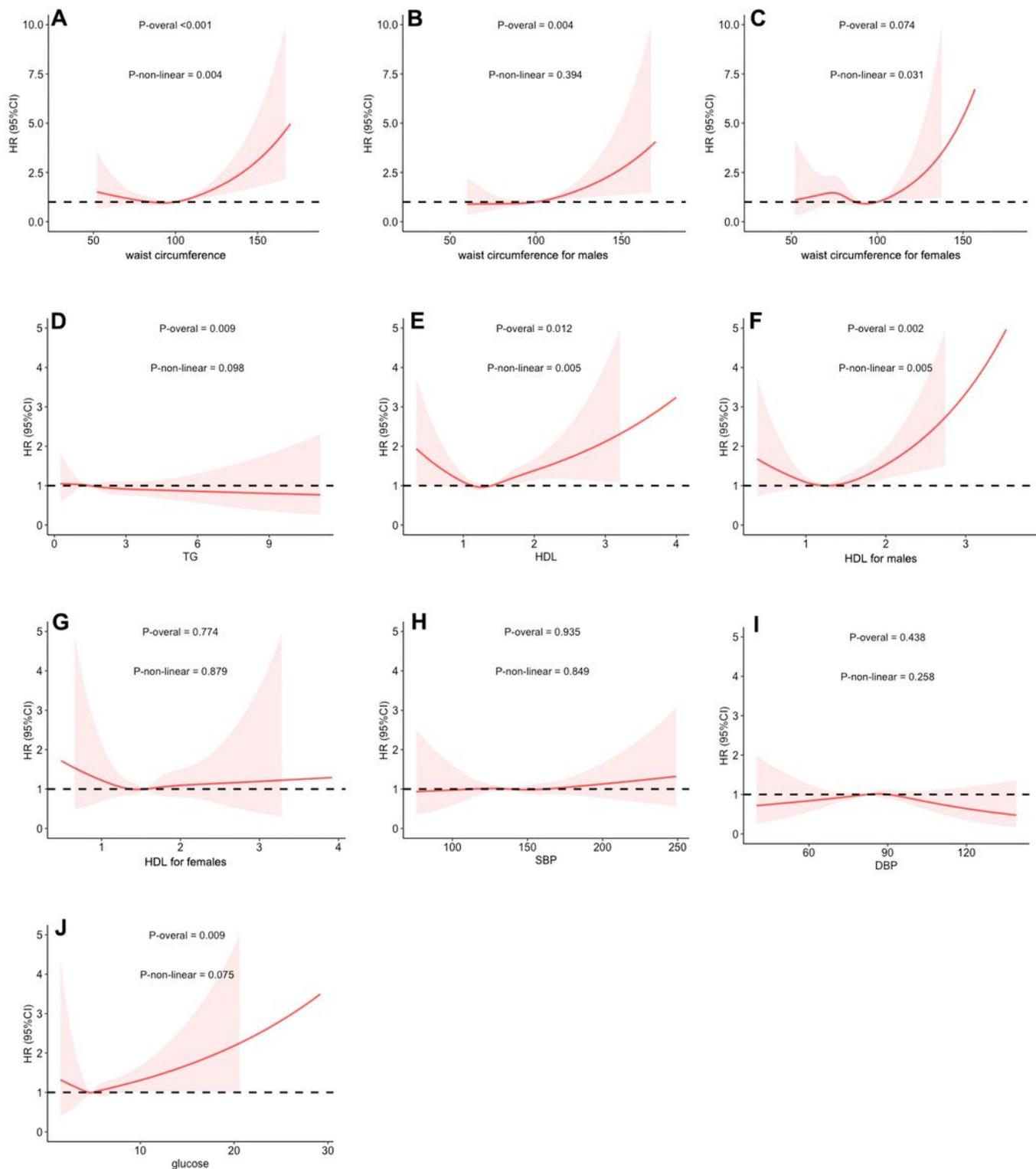


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