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Associations of combined lifestyle and metabolic risks with cancer incidence in the UK biobank study

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Abstract

Background Although metabolic syndrome (MetS) is associated with an increased risk of various cancers, the combined impact of MetS and healthy lifestyle factors (HLF) on cancer risk is unclear. This study aimed to investigate the independent and combined effects of MetS and HLF on the risk of 16 site-specific cancers in a large community-based cohort.

Methods A total of 289,557 participants in the UK Biobank were analyzed. MetS was defined using a combination of metabolic factors, while HLF scores were evaluated based on lifestyle behaviors, such as smoking, alcohol consumption, physical activity, and diet. Cox proportional hazard models were used to investigate the relationship between MetS or HLF and cancer risk, adjusting for age, sex, ethnicity, education level, family history of cancer, and the Townsend Deprivation Index (TDI).

Results During a median follow-up of 11.69 years, 11,190 individuals developed cancer. MetS was associated with an increased risk of 9 cancers in men and 7 cancers in women. Compared with participants with unfavorable lifestyles, regardless of metabolic status, HLF was significantly associated with decreased risk of overall cancer (without MetS: HR: 0.812; 95% CI: 0.745–0.886 for intermediate lifestyle and HR: 0.757; 95% CI: 0.669–0.855 for favorable lifestyle; with MetS: HR: 0.702; 95% CI: 0.572–0.862 for favorable lifestyle) and oesophagus, stomach, liver, lung, bronchus, trachea cancers in men and of lung, bronchus, trachea cancers in women. Our analysis demonstrated that the protective association between HLF and reduced cancer risk was confined to subgroups without MetS. Specifically, this association was observed for cancers of the lip, oral cavity, pharynx, colon, rectum, pancreas, kidney, bladder, and lymphoid leukemia in men, and for overall cancer in women(HR: 0.917; 95% CI: 0.862–0.975 for intermediate lifestyle and HR: 0.875; 95% CI: 0.817–0.938 for favorable lifestyle).

Conclusion MetS elevates risks for multiple cancers, while adopting a healthy lifestyle reduces risks of oesophagus, stomach, and lung, bronchus, trachea cancers in men and lung, bronchus, trachea cancer in women, regardless of

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metabolic status. However, MetS counteracts lifestyle-mediated protection against specific cancers—including lip, oral cavity, pharynx, colon, rectum, pancreas, kidney, and bladder cancers in men, as well as pancreas and breast cancers in women. These findings underscore the necessity to develop metabolic status-stratified management strategies and implement proactive prevention of MetS.

Keywords Metabolic syndrome, Lifestyle, Cancer incidence

Background

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including abdominal obesity, insulin resistance, hypertension, hyperglycemia, and hyperlipidemia [1, 2], which increase the risk of cardiovascular disease, type 2 diabetes, and other related disorders [3]. Several studies have shown that MetS is only associated with traditional cardiovascular diseases and the occurrence of various cancers, such as colon, rectum cancer, pancreas cancer, breast cancer, liver cancer, and endometrial cancer [4, 5]. Previous studies have demonstrated that MetS is significantly associated with various cancers, elucidating the mechanisms by which metabolic abnormalities, such as chronic inflammation [6], insulin resistance, lipid metabolism disorders, and oxidative stress [7, 8], contribute to tumorigenesis.

Although previous research showed that MetS is associated with increased cancer risk, further systematic studies should assess the specific benefits of lifestyle interventions in reducing cancer risk among individuals with MetS [9]. Nonetheless, studies have shown that a healthy diet and physical activity can reduce the risk of cancer [10, 11], but the effects of these interventions in further reducing cancer risk in MetS patients have not been fully validated [12]. Therefore, further studies are needed to guide cancer prevention strategies for individuals with MetS.

This study aimed to systematically assess the relationship between MetS and the risk of 16 specific cancers and explore the potential moderating effect of a healthy lifestyle on this association based on large-scale prospective cohort data. Therefore, this study may provide scientific evidence for the development of more effective cancer prevention measures.

Methods

Study population

The UK Biobank is a large-scale, prospective cohort study with over 500,000 participants recruited between 2006 and 2010 from various regions, including England, Wales, and Scotland. The study design and data collection methods have been described in detail in previous publications [13]. Extensive baseline questionnaires, interviews, and physical measurements were used to obtain lifestyle and other potentially health-related aspects of participants. Ethical approval for the UK Biobank cohort was granted by the North West Multicenter Research Ethics Committee, and all participants provided written informed consent [13]. UK Biobank data are available for researchers after acceptance of a research proposal. The present study was conducted under application number 92,668 of the UK Biobank resource.

Assessment of healthy lifestyle factors

We used data on smoking, physical activity and diet to calculate adherence scores. Food Frequency Questionnaire (FFQ) data were used to assess adherence to "Eat a diet rich in wholegrains, vegetables, fruit, and beans", "Limit consumption of red and processed meat" and "Limit alcohol consumption". Self-reported time spent in Moderate to Vigorous Physical Activity (MVPA), collected via the short form of the International Physical Activity Questionnaire (IPAQ) [14], was used to assess adherence with the physical activity guidelines. We calculated adherence scores using data on smoking, physical activity, and diet. Details on the physical training, limit alcohol consumption and diet score construction and cutoff values used are described in Supplementary Table S1 and were elaborated earlier by Romaguera and colleagues [15].

The participants were assigned scores for smoking, alcohol consumption, physical activity and consumption of red and processed meat as follows: 1 points for optimal behaviors, 0.5 points for moderate behaviors, and 0 points for unhealthy behaviors. For sub-components ("Eat a diet rich in fibre" and "Eat a diet rich in fruits and vegetables"), 0.5 points for optimal behaviors, 0.25 points for moderate behaviors, and 0 points for unhealthy behaviors. The final score ranged from 0 to 5.

Assessment of metabolic status

MetS was defined according to a consensus criteria, incorporating five key metabolic abnormalities: elevated blood pressure (systolic blood pressure (BP) ≥ 130 mm Hg, diastolic BP ≥ 85 mm Hg, or both), hypertriglyceridemia (≥ 1.7 mmol/L), low high-density lipoprotein cholesterol (HDL-C) levels (male: < 1.0 mmol/L; female: < 1.3 mmol/L), increased waist circumference (male: ≥ 102 cm; female: ≥ 88 cm for European populations), and hyperglycemia (fasting glucose ≥ 100 mg/dL) [16]. Two measurements of systolic and diastolic blood pressure (BP) were taken and averaged for further analysis. Waist circumference was measured at the natural indent (or umbilicus if the natural indent could not be located) using a Seca 200

tape measure. Enzyme immunoinhibition and glycerol-3-phosphate-peroxidase methods were used to determine serum triglyceride and HDL-C concentrations. Glycated hemoglobin (HbA1c) was utilized to assess hyperglycemia instead of fasting glucose levels, as most participants in the UK Biobank had non-fasting glucose measurements. A cutoff value of ≥42.0 mmol/mol was applied to indicate impaired glucose regulation [17, 18]. MetS was diagnosed when participants exhibited any three of the aforementioned components.

Outcome ascertainment

Incident cancer cases in the UK Biobank were identified through electronic linkage with the National Health Service (NHS) central registers and death registries for England, Wales, and Scotland. For England and Wales, the Cancer Registry data was up to December 31, 2020; and November 30, 2021 for Scotland. The cancers were classified according to the International Classification of Diseases, 10th Revision (ICD-10). Herein, we focused on cancers diagnosed post-UK Biobank recruitment, specifically targeting 16 cancers for which MetS or healthy lifestyle factors (HLF) is considered an etiological factor: lip, oral cavity, pharynx (C00–C14), oesophagus (C15), stomach (C16), colon, rectum(C18–C20), liver (C22), pancreas (C25), lung, bronchus, trachea (C33–C34), skin melanoma (C43), breast (C50), corpus uteri (C54–C55), ovary (C56), kidney (C64), bladder (C67), brain and central nervous system (C70–C72), multiple myeloma (C90), and lymphoid leukemia (C91). Participants were censored if they were diagnosed with cancer at other sites (excluding non-melanoma skin cancer) before the diagnosis of the target cancer.

Assessment of covariates

Sociodemographic data, including sex, ethnicity, and family history of cancer, were collected through a self-reported touchscreen questionnaire during the baseline assessment at the recruitment centers. Age was calculated based on the reported date of birth. The TDI, an area-based measure of socioeconomic deprivation incorporating factors, such as unemployment, overcrowding, non-car ownership, and non-home ownership, was calculated using each postcode at the time of recruitment based on data from the most recent national census [19]. Education level, a key indicator of socioeconomic status, was self-reported during the baseline assessment and categorized according to the highest level of education attained. All models were adjusted for age, ethnicity, family history of cancer, TDI, and education since these covariates influence both cancer risk and health behaviors.

Statistical analysis

Cancer risk among UK Biobank participants was assessed from baseline until the earliest occurrence of cancer diagnosis, death, loss to follow-up, or the end of the follow-up period. The associations between MetS/HLF scores and cancer incidence were assessed using multivariable Cox proportional hazards regression models, with hazard ratios (HRs) and 95% confidence intervals (CIs). The Cox regression models were adjusted for age at inclusion, ethnicity, education, family history of cancer, and the Townsend Deprivation Index (TDI). For female-specific cancers (breast, corpus uteri, and ovary), additional adjustments were made for menopausal status, use of oral contraceptives, hormone replacement therapy, age at menarche, age at first birth, and parity. The participants were categorized into favorable (highest tertile), intermediate (middle tertile), and unfavorable (lowest tertile) lifestyle groups based on their HLF scores. The cross-product terms between metabolic status (with/without MetS) and lifestyle groups (favorable/intermediate/ unfavorable lifestyle) were incorporated into the Cox regression models. Interaction significance was evaluated using the likelihood ratio test (LRT), comparing models with and without interaction terms. Subgroup analyses stratified by metabolic status groups were also performed. Missing data for any covariates were addressed using multiple imputation. Incident cancer cases occurring within the first year after baseline were excluded from the joint analysis. All statistical tests were two-sided. P-values < 0.05 were considered statistically significant. R software (version 4.3.2, R Project for Statistical Computing) was used for statistical analyses.

Results

Baseline characteristics of the study population

A total of 289,557 UK Biobank participants were included in this study. The characteristics of the participants are described in Table 1. A total of 11,190 participants developed cancer, including 3,733 males and 7,457 females, during a median follow-up of 11.69 years (IQR: 10.93–12.45).

The association between metabolic status and site-specific cancer risk

We included 16 predefined site-specific cancers for analysis. MetS was associated with an increased risk of overall cancer in both men (HR:1.315;95%CI:1.228–1.407) and women (HR:1.181;95%CI:1.120–1.247) after adjusting for some factors, including age, ethnicity, family history of cancer, TDI, and education (Table 2). Additionally, MetS was significantly associated with oesophagus, stomach, colon, rectum, pancreas, lung, bronchus, trachea, breast, corpus uteri, kidney cancer, multiple myeloma, and lymphoid leukemia.

Table 1 Baseline characteristics of participants

	Overall (*N* = 289557)	Non-incident Cancer (*N* = 278367)	Incident Cancer (*N* = 11190)	*P* value
Age (years)	56.1 (8.1)	56.0 (8.1)	58.6 (7.5)	< 0.001
Sex				
Men	140,725 (48.6%)	136,992 (49.2%)	3733 (33.4%)	< 0.001
Women	148,832 (51.4%)	141,375 (50.8%)	7457 (66.6%)	
Townsend deprivation index				
1 (Least deprived)	58,123 (20.1%)	55,860 (20.1%)	2263 (20.2%)	0.0252
2–4	173,523 (59.9%)	166,722 (59.9%)	6801 (60.8%)	
5 (Most deprived)	57,911 (20.0%)	55,785 (20.0%)	2126 (19.0%)	
Educational qualifications				
College or above	101,746 (35.1%)	98,092 (35.2%)	3654 (32.7%)	< 0.001
High school or equivalent	145,977 (50.4%)	140,400 (50.4%)	5577 (49.8%)	
Less than high school	41,834 (14.4%)	39,875 (14.3%)	1959 (17.5%)	
Ethnicity				
Non-White	14,723 (5.1%)	14,372 (5.2%)	351 (3.1%)	< 0.001
White	274,834 (94.9%)	263,995 (94.8%)	10,839 (96.9%)	
Family history of cancer				
Yes	88,408 (30.5%)	84,674 (30.4%)	3734 (33.4%)	< 0.001
No	201,149 (69.5%)	193,693 (69.6%)	7456 (66.6%)	
HLF scores	2.751 (0.823)	2.751 (0.823)	2.758 (0.820)	0.417
Met status				
Without MetS	211,402 (75.9%)	219,466 (75.8%)	8064 (72.1%)	< 0.001
With MetS	66,965 (24.1%)	70,091 (24.2%)	3126 (27.9%)	

Data are presented as means and standard deviation in brackets (SD) for total score and age. Data for sex, Townsend deprivation index, education, ethnicity, family history of cancer and Met status are presented as number of participants (*n*) and percentage in brackets (%)

Table 2 Association between metabolic status and site-specific cancer risk

ICD10	Cancer site	Men		Women	
		Hazard Ratio (95%CI)	*P*-value	Hazard Ratio (95%CI)	*P*-value
C00-C14	Lip, Oral Cavity, Pharynx	1.029 [0.815, 1.299]	0.812	0.990 [0.681, 1.439]	0.957
C15	**Oesophagus**	1.446 [1.186, 1.764]	**< 0.001**	0.907 [0.599, 1.375]	0.646
C16	**Stomach**	1.503 [1.173, 1.926]	**0.001**	1.418 [0.958, 2.099]	0.081
C18-C20	**Colon**, **Rectum**	1.241 [1.125, 1.369]	**< 0.001**	1.227 [1.083, 1.391]	**0.001**
C25	**Pancreas**	1.321 [1.069, 1.632]	**0.01**	1.543 [1.204, 1.976]	**0.001**
C33-C34	**Lung**, **Bronchus**, **Trachea**	1.141 [1.006, 1.293]	**0.04**	1.407 [1.222, 1.621]	**< 0.001**
C43	Skin Melanoma	0.993 [0.854, 1.154]	0.923	0.966 [0.808, 1.156]	0.706
C50	**Breast**			1.141 [1.069, 1.217]	**< 0.001**
C54-C55	**Corpus Uteri**, **Nos**			2.235 [1.932, 2.586]	**< 0.001**
C56	Ovary			1.078 [0.878, 1.325]	0.472
C64	**Kidney**	1.480 [1.230, 1.779]	**< 0.001**	2.326 [1.783, 3.035]	**< 0.001**
C67	Bladder	1.175 [0.972, 1.420]	0.095	1.215 [0.831, 1.778]	0.315
C70-C72	Brain, Central Nerves	0.988 [0.747, 1.306]	0.932	0.853 [0.587, 1.240]	0.405
C90	**Multiple Myeloma**	1.276 [1.005, 1.621]	**0.046**	1.076 [0.776, 1.490]	0.661
C91	**Lymphoid Leukaemia**	1.376 [1.070, 1.768]	**0.013**	1.193 [0.828, 1.717]	0.343
	Overall Cancer	1.265 [1.179, 1.358]	**< 0.001**	1.173 [1.111, 1.238]	**< 0.001**

Hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazards regression models, adjusted for age, ethnicity, family cancer history, Townsend deprivation index, and education. For female-specific cancers (breast, corpus uteri, and ovary cancers), the models were further adjusted for menopausal status, use of oral contraceptives, use of hormone replacement therapy, age at menarche, age at first birth, and parity

Specifically, colon, rectum cancer (Men: HR:1.241; 95%CI:1.125–1.369; Women: HR:1.227; 95% CI: 1.083–1.391), liver cancer (Men: HR:2.261; 95%CI:1.744–2.931; Women: HR:1.799; 95% CI: 1.199–2.699), pancreas cancer (Men: HR:1.321; 95%CI:1.069–1.632; Women: HR:1.543; 95%CI:1.204–1.976), lung, bronchus, trachea cancer (Men: HR:1.141; 95% CI: 1.006–1.293; Women: HR:1.407; 95% CI: 1.222–1.621), and kidney cancer (Men: HR:1.480; 95% CI: 1.230–1.779; Women: HR:2.326; 95% CI: 1.783–3.035) were significantly associated with MetS in both men and women. Notably, MetS was significantly associated with oesophagus

cancer (HR:1.446; 95%CI:1.186–1.764), stomach cancer (HR:1.503 95%CI:1.173–1.926), multiple myeloma (HR:1.276; 95%CI:1.005–1.621), and lymphoid leukemia (HR:1.376; 95%CI:1.070–1.768) in men; while breast cancer (HR:1.141; 95%CI:1.069–1.217) and corpus uteri cancer (HR:2.235; 95%CI:1.932–2.586) were significantly associated with MetS in women. Liver cancer in Men (HR:2.261; 95%CI:1.744–2.931) and kidney cancer in women (HR:2.326; 95%CI:1.783–3.035) exhibited the highest hazard ratios within each sex group.

The association between Lifestyle factors and site-specific cancer risk

Overall cancer risk was associated with smoking, physical activity, meat intake and fibre intake in males, and with smoking, physical activity, and fiber intake in females (Additional file 1: Supplementary Table S2). Notably, in males, the most significant reduction in overall cancer risk was associated with never smoking (HR:0.638; 95% CI: 0.577–0.705), while in females, it was associated with sufficient fiber intake (HR:0.802; 95% CI: 0.647–0.995). A comprehensive HLF score was derived by aggregating individual lifestyle scores. When the HLF score was treated as a continuous variable, each one-point increase in the lifestyle score was associated with a decrease in overall cancer risk (Men: HR: 0.875; 95% CI: 0.840–0.910; Women: HR: 0.936; 95% CI: 0.909–0.963) (Additional file 1: Supplementary Table S3).

Participants were categorized into favorable (highest score tertile), intermediate (middle score tertile), and unfavorable lifestyles groups (lowest score tertile). The HRs for participants with intermediate and favorable lifestyles, compared to those with an unfavorable lifestyle, are presented in Supplementary Table S4 for men and Supplementary Table S5 for women. Compared to participants maintaining unfavorable lifestyles in model 2, in men, those adopting intermediate lifestyles demonstrated a statistically significant reduction in overall cancer risk (HR: 0.865; 95%CI: 0.807–0.927), with pronounced protective effects notably observed for cancers of the lip, oral cavity, pharynx (HR: 0.647; 95%CI: 0.510–0.819), oesophagus(HR: 0.581; 95%CI: 0.468–0.722), colon, rectum(HR: 0.827; 95%CI: 0.749–0.914), liver (HR: 0. 666; 95%CI: 0. 504–0.879), pancreas(HR: 0.789; 95%CI: 0.636–0.979), lung, bronchus, trachea(HR: 0.442; 95%CI: 0.385–0.509), and bladder cancers(HR: 0.725; 95%CI: 0.595–0.882). Notably, the protective effects intensified and broadened with progression to favorable lifestyles. Compared to participants maintaining unfavorable lifestyles in model 2, in men, those maintaining favorable lifestyles exhibited further reduced risks for all cancers combined (HR: 0.769; 95%CI: 0.691–0.855) and specific cancers: lip, oral cavity, pharynx(HR: 0.517; 95%CI: 0.357–0.748), oesophagus (HR: 0.516; 95%CI: 0.369–0.720), stomach (HR: 0.511; 95%CI: 0.328–0.796), colon, rectum (HR: 0.643; 95%CI: 0.551–0.751), pancreas (HR: 0.508; 95%CI: 0.353–0.731), liver (HR: 0. 238; 95%CI: 0. 129–0. 441), lung, bronchus, trachea (HR: 0.218; 95%CI: 0.164–0.291), kidney (HR: 0.637; 95%CI: 0.470–0.864), and bladder cancers (HR: 0.742; 95%CI: 0.561–0.983) (Supplementary Table S4).

In model 2, participants adopting intermediate lifestyles showed reduced all cancers combined risk (HR: 0.917; 95%CI:0.870–0.967) in women, particularly for pancreas (HR: 0.674; 95%CI:0.516–0.880) and lung, bronchus, trachea cancers (HR: 0.473; 95%CI:0.409–0.548), with modest breast cancer protection (HR: 0.912; 95%CI:0.857–0.971). Progression to favorable lifestyles amplified protection, yielding stronger reductions for all cancers (HR: 0.878; 95%CI: 0.828–0.932) and specific cancers: pancreas (HR: 0.693; 95%CI: 0.517–0.930), lung, bronchus, trachea (HR: 0.308; 95%CI: 0.254–0.375) and breast cancers (HR: 0.833; 95%CI: 0.775–0.894) (Supplementary Table S5).

Joint effect of lifestyle factors and metabolic status on overall cancer risk

In further stratification analyses by metabolic status with unfavorable lifestyles as the reference group, based on the model 2, we confirmed that among participants without metabolic syndrome, healthy lifestyles were significantly associated with a decreased risk of overall cancer (HR: 0.812; 95% CI: 0.745–0.886 for intermediate lifestyle and HR: 0.757; 95% CI: 0.669–0.855 for favorable lifestyle) in men (Table 3). However, among participants with metabolic syndrome, significant cancer risk reduction was observed only in those maintaining a favorable lifestyle (HR: 0.702; 95% CI: 0.572–0.862) in men. In subsequent analyses, we confirmed that in model 2, regardless of metabolic status, participants with healthier lifestyles had a reduced risk of oesophagus, stomach, liver, lung, bronchus, trachea cancers compared to those with unfavorable lifestyles in men. Notably, our analysis revealed that the protective associations between healthier lifestyles and reduced risks were exclusively observed in the subgroup without metabolic syndrome, compared to participants with unfavorable lifestyles, for cancers of the lip, oral cavity, pharynx (HR: 0.508; 95% CI: 0.380–0.679 for intermediate lifestyle and HR: 0.463; 95% CI: 0.303–0.709 for favorable lifestyle), colon, rectum (HR: 0.789; 95% CI: 0.698–0.891 for intermediate lifestyle and HR: 0.574; 95% CI: 0.475–0.694 for favorable lifestyle), pancreas (HR: 0.812; 95% CI: 0.745–0.886 for intermediate lifestyle and HR: 0.723; 95% CI: 0.553–0.945 for favorable lifestyle), kidney (HR: 0.645; 95% CI: 0.446–0.933 for favorable lifestyle), bladder (HR: 0.688; 95% CI: 0.541–0.874 for intermediate lifestyle and HR: 0.664; 95% CI: 0.472–0.933 for

Table 3 Associations of lifestyle factors with cancer across metabolic status groups in men

lifestyle category	Without MetS			With MetS			*p* for interaction
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	
Overall							**0.003**
No.of cases /Person-years	1204/501,378	891/447,345	330/186,317	727/236,032	475/144,710	112/49,947	
Hazard Ratio (95%CI)	Ref.	0.812 [0.745, 0.886]	0.757 [0.669, 0.855]	Ref.	1.025 [0.913, 1.151]	0.702 [0.572, 0.862]	
P-value		**< 0.001**	**< 0.001**		0.68	**0.001**	
Lip, Oral Cavity, Pharynx							**0.010**
No.of cases /Person-years	151/501,378	66/447,345	25/186,317	56/236,032	38/144,710	8/49,947	
Hazard Ratio (95%CI)	Ref.	0.508 [0.380, 0.679]	0.463 [0.303, 0.709]	Ref.	1.117 [0.739, 1.689]	0.684 [0.324, 1.443]	
P-value		**< 0.001**	**< 0.001**		0.599	0.318	
Oesophagus							0.571
No.of cases /Person-years	153/501,378	76/447,345	30/186,317	105/236,032	45/144,710	10/49,947	
Hazard Ratio (95%CI)	Ref.	0.550 [0.418, 0.725]	0.545 [0.368, 0.807]	Ref.	0.683 [0.481, 0.969]	0.496 [0.259, 0.950]	
P-value		**< 0.001**	**0.002**		**0.033**	**0.034**	
Stomach							**0.002**
No.of cases /Person-years	89/501,378	52/447,345	20/186,317	54/236,032	48/144,710	3/49,947	
Hazard Ratio (95%CI)	Ref.	0.650 [0.461, 0.916]	0.616 [0.378, 1.003]	Ref.	1.381 [0.935, 2.040]	0.252 [0.078, 0.810]	
P-value		**0.014**	0.051		0.105	**0.021**	
Colon, Rectum							**0.037**
No.of cases/Person-years	622/501,378	450/447,345	131/186,317	344/236,032	204/144,710	62/49,947	
Hazard Ratio (95%CI)	Ref.	0.789 [0.698, 0.891]	0.574 [0.475, 0.694]	Ref.	0.940 [0.790, 1.118]	0.887 [0.676, 1.165]	
P-value		**< 0.001**	**< 0.001**		0.486	0.389	
Liver							0.140
No.of cases /Person-years	71/501,378	38/447,345	9/186,317	73/236,032	39/144,710	2/49,947	
Hazard Ratio (95%CI)	Ref.	0.613 [0.413, 0.910]	0.344 [0.171, 0.691]	Ref.	0.817 [0.553, 1.207]	0.120 [0.029, 0.493]	
P-value		**0.015**	**0.003**		0.31	**0.003**	
Pancreas							0.264
No.of cases /Person-years	135/501,378	90/447,345	22/186,317	76/236,032	47/144,710	12/49,947	
Hazard Ratio (95%CI)	Ref.	0.723 [0.553, 0.945]	0.436 [0.277, 0.685]	Ref.	0.979 [0.680, 1.409]	0.760 [0.412, 1.404]	
P-value		**0.018**	**< 0.001**		0.907	0.381	
Lung, Bronchus, Trachea							**0.007**
No.of cases /Person-years	507/501,378	172/447,345	30/186,317	267/236,032	93/144,710	20/49,947	
Hazard Ratio (95%CI)	Ref.	0.401 [0.337, 0.477]	0.173 [0.120, 0.251]	Ref.	0.547 [0.432, 0.693]	0.356 [0.225, 0.562]	
P-value		**< 0.001**	**< 0.001**		**< 0.001**	**< 0.001**	
Skin Melanoma							0.386
No.of cases /Person-years	259/501,378	259/447,345	98/186,317	113/236,032	97/144,710	26/49,947	
Hazard Ratio (95%CI)	Ref.	1.079 [0.908, 1.283]	1.042 [0.825, 1.315]	Ref.	1.343 [1.023, 1.762]	1.165 [0.761, 1.786]	
P-value		0.386	0.732		**0.033**	0.482	

Table 3 (continued)

lifestyle category	Without MetS			With MetS			*p* for interaction
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	
Kidney							0.742
No.of cases /Person-years	151/501,378	117/447,345	35/186,317	104/236,032	66/144,710	15/49,947	
Hazard Ratio (95%CI)	Ref.	0.858 [0.674, 1.094]	0.645 [0.446, 0.933]	Ref.	1.016 [0.746, 1.384]	0.695 [0.403, 1.200]	
P-value		0.217	**0.02**		0.92	0.192	
Bladder							0.321
No.of cases /Person-years	176/501,378	109/447,345	41/186,317	94/236,032	50/144,710	19/49,947	
Hazard Ratio (95%CI)	Ref.	0.688 [0.541, 0.874]	0.664 [0.472, 0.933]	Ref.	0.823 [0.584, 1.161]	0.996 [0.607, 1.636]	
P-value		**0.002**	**0.018**		0.267	0.988	
Brain, Central Nerves							0.103
No.of cases /Person-years	65/501,378	80/447,345	31/186,317	43/236,032	19/144,710	8/49,947	
Hazard Ratio (95%CI)	Ref.	1.371 [0.987, 1.903]	1.326 [0.863, 2.038]	Ref.	0.681 [0.396, 1.170]	0.775 [0.359, 1.673]	
P-value		0.06	0.197		0.164	0.516	
Multiple Myeloma							0.576
No.of cases /Person-years	76/501,378	89/447,345	36/186,317	54/236,032	39/144,710	10/49,947	
Hazard Ratio (95%CI)	Ref.	1.244 [0.915, 1.691]	1.255 [0.843, 1.869]	Ref.	1.120 [0.741, 1.694]	0.782 [0.394, 1.552]	
P-value		0.163	0.264		0.59	0.481	
Lymphoid Leukaemia							**0.010**
No.of cases /Person-years	86/501,378	53/447,345	36/186,317	47/236,032	41/144,710	8/49,947	
Hazard Ratio (95%CI)	Ref.	0.679 [0.481, 0.957]	1.160 [0.785, 1.715]	Ref.	1.363 [0.896, 2.075]	0.810 [0.381, 1.722]	
P-value		**0.027**	0.457		0.148	0.584	

Hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazards regression models, adjusted for age, ethnicity, family cancer history, Townsend deprivation index, and education. For female-specific cancers (such as breast, uterine, and ovarian cancers), the models were further adjusted for menopausal status, use of oral contraceptives, use of hormone replacement therapy, age at menarche, age at first birth, and parity

Table 4 Associations of lifestyle factors with cancer across metabolic status groups in women

lifestyle category	Without MetS			With MetS			*p* for interaction
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	
Overall							0.647
No.of cases /Person-years	1880/427,119	2271/544,645	1488/372,210	692/130,262	691/132,576	435/84,783	
Hazard Ratio (95%CI)	Ref.	0.917 [0.862, 0.975]	0.875 [0.817, 0.938]	Ref.	0.940 [0.846, 1.046]	0.921 [0.815, 1.040]	
P-value		**0.006**	**< 0.001**		0.256	0.185	
Lip, Oral Cavity, Pharynx							0.672
No.of cases /Person-years	31/427,119	62/544,645	37/372,210	13/130,262	14/132,576	9/84,783	
Hazard Ratio (95%CI)	Ref.	1.548 [1.004, 2.386]	1.364 [0.843, 2.205]	Ref.	1.004 [0.470, 2.145]	0.979 [0.412, 2.329]	
P-value		**0.048**	0.206		0.993	0.962	
Oesophagus							0.942
No.of cases /Person-years	29/427,119	39/544,645	37/372,210	10/130,262	11/132,576	8/84,783	
Hazard Ratio (95%CI)	Ref.	0.941 [0.581, 1.524]	1.273 [0.780, 2.076]	Ref.	1.038 [0.439, 2.455]	1.229 [0.481, 3.138]	
P-value		0.805	0.334		0.932	0.666	
Stomach							0.428
No.of cases /Person-years	20/427,119	38/544,645	22/372,210	16/130,262	14/132,576	8/84,783	
Hazard Ratio (95%CI)	Ref.	1.335 [0.776, 2.298]	1.104 [0.601, 2.029]	Ref.	0.798 [0.387, 1.644]	0.598 [0.248, 1.443]	
P-value		0.297	0.75		0.54	0.253	
Colon, Rectum							0.865
No.of cases/Person-years	282/427,119	402/544,645	268/372,210	124/130,262	132/132,576	88/84,783	
Hazard Ratio (95%CI)	Ref.	1.032 [0.885, 1.202]	0.969 [0.819, 1.147]	Ref.	0.973 [0.760, 1.245]	1.008 [0.764, 1.331]	
P-value		0.69	0.714		0.827	0.952	
Liver							0.194
No.of cases /Person-years	25/427,119	28/544,645	13/372,210	15/130,262	11/132,576	12/84,783	
Hazard Ratio (95%CI)	Ref.	0.806 [0.469, 1.385]	0.531 [0.271, 1.043]	Ref.	0.652 [0.298, 1.424]	1.063 [0.490, 2.305]	
P-value		0.435	0.066		0.283	0.878	
Pancreas							0.889
No.of cases /Person-years	71/427,119	72/544,645	54/372,210	43/130,262	31/132,576	22/84,783	
Hazard Ratio (95%CI)	Ref.	0.709 [0.510, 0.985]	0.729 [0.510, 1.042]	Ref.	0.648 [0.407, 1.030]	0.677 [0.400, 1.145]	
P-value		**0.04**	0.083		0.067	0.145	
Lung, Bronchus, Trachea							0.162
No.of cases /Person-years	318/427,119	202/544,645	84/372,210	161/130,262	87/132,576	47/84,783	
Hazard Ratio (95%CI)	Ref.	0.464 [0.389, 0.554]	0.271 [0.213, 0.346]	Ref.	0.512 [0.394, 0.665]	0.426 [0.306, 0.592]	
P-value		**< 0.001**	**< 0.001**		**< 0.001**	**< 0.001**	
Skin Melanoma							**0.018**
No.of cases /Person-years	183/427,119	247/544,645	185/372,210	59/130,262	70/132,576	24/84,783	
Hazard Ratio (95%CI)	Ref.	1.027 [0.848, 1.244]	1.160 [0.945, 1.425]	Ref.	1.116 [0.788, 1.582]	0.620 [0.385, 1.000]	
P-value		0.783	0.156		0.536	**0.05**	

Table 4 (continued)

lifestyle category	Without MetS			With MetS			*p* for interaction
	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	Unfavorable lifestyle	Intermediate lifestyle	Favorable lifestyle	
Breast							0.217
No.of cases /Person-years	1275/427,119	1502/544,645	943/372,210	421/130,262	437/132,576	269/84,783	
Hazard Ratio (95%CI)	Ref.	0.910 [0.844, 0.981]	0.837 [0.769, 0.912]	Ref.	0.996 [0.871, 1.140]	0.970 [0.830, 1.134]	
P-value		**0.014**	**< 0.001**		0.958	0.702	
Corpus Uteri, Nos							**0.030**
No.of cases /Person-years	150/427,119	176/544,645	144/372,210	82/130,262	124/132,576	73/84,783	
Hazard Ratio (95%CI)	Ref.	0.855 [0.687, 1.064]	0.968 [0.768, 1.221]	Ref.	1.412 [1.066, 1.871]	1.203 [0.870, 1.663]	
P-value		0.161	0.786		**0.016**	0.263	
Ovary							0.244
No.of cases /Person-years	109/427,119	159/544,645	100/372,210	40/130,262	38/132,576	35/84,783	
Hazard Ratio (95%CI)	Ref.	1.105 [0.865, 1.412]	0.985 [0.748, 1.296]	Ref.	0.905 [0.579, 1.415]	1.268 [0.796, 2.019]	
P-value		0.424	0.914		0.662	0.318	
Kidney							0.870
No.of cases /Person-years	47/427,119	54/544,645	36/372,210	41/130,262	32/132,576	22/84,783	
Hazard Ratio (95%CI)	Ref.	0.831 [0.561, 1.230]	0.807 [0.521, 1.249]	Ref.	0.701 [0.440, 1.116]	0.728 [0.429, 1.235]	
P-value		0.355	0.335		0.134	0.239	
Bladder							0.582
No.of cases /Person-years	32/427,119	32/544,645	27/372,210	18/130,262	14/132,576	7/84,783	
Hazard Ratio (95%CI)	Ref.	0.718 [0.439, 1.174]	0.836 [0.499, 1.403]	Ref.	0.683 [0.338, 1.380]	0.485 [0.198, 1.188]	
P-value		0.186	0.499		0.288	0.113	
Brain, Central Nerves							0.151
No.of cases /Person-years	40/427,119	65/544,645	39/372,210	14/130,262	9/132,576	12/84,783	
Hazard Ratio (95%CI)	Ref.	1.205 [0.812, 1.790]	1.030 [0.660, 1.607]	Ref.	0.597 [0.257, 1.384]	1.315 [0.604, 2.865]	
P-value		0.354	0.897		0.229	0.49	
Multiple Myeloma							0.943
No.of cases /Person-years	55/427,119	57/544,645	41/372,210	19/130,262	18/132,576	12/84,783	
Hazard Ratio (95%CI)	Ref.	0.747 [0.515, 1.084]	0.739 [0.491, 1.113]	Ref.	0.823 [0.431, 1.573]	0.822 [0.394, 1.713]	
P-value		0.125	0.147		0.556	0.6	
Lymphoid Leukaemia							0.170
No.of cases /Person-years	34/427,119	44/544,645	30/372,210	10/130,262	15/132,576	16/84,783	
Hazard Ratio (95%CI)	Ref.	0.899 [0.574, 1.409]	0.846 [0.515, 1.389]	Ref.	1.322 [0.592, 2.953]	2.045 [0.912, 4.586]	
P-value		0.643	0.509		0.496	0.082	

Hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazards regression models, adjusted for age, ethnicity, family cancer history, Townsend deprivation index, and education. For female-specific cancers (such as breast, uterine, and ovarian cancers), the models were further adjusted for menopausal status, use of oral contraceptives, use of hormone replacement therapy, age at menarche, age at first birth, and parity

favorable lifestyle), and lymphoid leukaemia (HR: 0.679; 95% CI: 0.481–0.957 for intermediate lifestyle).

HLF demonstrated protective effects in lung, bronchus, trachea cancers in women irrespective of metabolic status. However, in women we only observed an association between a healthy lifestyle and a reduced risk of overall cancer combined (HR: 0.917; 95% CI: 0.862–0.975 for intermediate lifestyle and HR: 0.875; 95% CI: 0.817–0.938 for favorable lifestyle) with pancreas (HR: 0.709; 95% CI: 0.510–0.985 for intermediate lifestyle), and breast cancers(HR: 0.910; 95% CI: 0.844–0.981 for intermediate lifestyle and HR: 0.837; 95% CI: 0.769–0.912 for favorable lifestyle) in participants without MetS, but no such effect was detected in participants with MetS (Table 4).

Statistically significant interactions were observed between metabolic status and lifestyle groups in relation to the risk of overall cancer (p for interaction = 0.003), lip, oral cavity, pharynx (p for interaction = 0.010), stomach (p for interaction = 0.002), colon, rectum (p for interaction = 0.037), lung, bronchus, trachea (p for interaction = 0.007), lymphoid leukaemia (p for interaction = 0.010) in men. No statistically significant interaction effects were observed in the aforementioned cancers in women.

Exceptions were seen for skin melanoma, lip, oral cavity, pharynx, and corpus uteri cancer. Participants with MetS and intermediate lifestyle exhibited significantly elevated risks of skin melanoma in men, lip, oral cavity, pharynx cancer in women without MetS, and corpus uteri cancer in women with MetS.

Discussion

MetS and HLF jointly influence cancer risk. In this study, we systematically assessed the individual and joint effects of metabolic status and HLF on 16 cancer types through sex-stratified analyses in a large community-based cohort. Results indicated that MetS was associated with an increased risk of 9 cancers in men and 7 cancers in women. A healthy lifestyle demonstrated generalized protective effects, showing significant risk reduction for overall, oesophagus, stomach, liver, and lung, bronchus, trachea cancers in men, as well as lung, bronchus, trachea cancer in women, irrespective of metabolic status. Notably, the protective associations against overall, lip, oral cavity, pharynx, colon, rectum, pancreas, kidney, bladder and lymphoid leukaemia cancers in men, and against overall, lip, oral cavity, pharynx, pancreas and breast cancers in women were exclusively observed in participants without MetS. Regardless of sex, participants without MetS demonstrated stronger inverse associations between HLF adherence and reduced cancer risk compared to those with MetS.

With growing understanding of metabolic health and disease pathogenesis, increasing attention has focused on the relationship between MetS and cancer risk [20–23]. Our research has established associations between MetS and elevated risks of various cancers. MetS demonstrates significant correlations with site-specific cancer risk elevation, particularly for cancers of the oesophagus, colon, rectum, pancreas, lung, breast, uterine corpus, and kidney, as well as lymphoid leukaemia and multiple myeloma. These findings align with previous studies [4, 5, 24–33]. Previous research by Harding J reported no association between MetS and elevated overall cancer risk [34]. Similarly, Bitzur R's study found no significant correlation between MetS and overall cancer risk in age- and sex-adjusted models [35]. In this study, we not only evaluated the independent and joint effects of MetS across 16 cancer types but additionally performed sex-stratified assessments for each individual malignancy [4, 34, 35]. Our findings confirm and expand prior evidence that MetS elevates cancer susceptibility, with systematic demonstration of its differential effects between sexes. These insights enhance individual awareness of MetS-associated cancer predisposition and reinforce proactive prevention strategies [23, 36].

Previous studies indicate that approximately 40% of cancers in the UK (United Kingdom) could be prevented annually through lifestyle modifications [37]. Studies by Marino and Malcomson have demonstrated that HLF adherence confers cancer-protective effects, with our results showing concordance with them [11, 38]. Further sex-stratified analyses showed that a healthy lifestyle was associated with a reduced risk of lip, oral cavity, pharynx cancer, oesophagus cancer, stomach cancer, colon cancer, rectal cancer, and kidney cancer, specifically in men. Additionally, a healthy lifestyle was related to a reduced risk of pancreas cancer, lung, bronchus, trachea cancer, and bladder cancer in men and women. The associations between HLF and cancer risk, exhibiting differential effects across sexes, may reflect the different relative distribution of the chosen cancers and the varying contributions of lifestyle factors across them [39].

Lifestyle patterns—including physical inactivity, tobacco use, alcohol consumption, and suboptimal dietary habits—constitute key modifiable drivers of obesity, type 2 diabetes mellitus, dyslipidemia, and MetS [40, 41]. In alignment with this evidence base, authoritative organizations including the American Cancer Society (ACS) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) have established evidence-based guidelines to mitigate cancer burden through population-level behavioral modification [42, 43]. Prior investigations have established associations between HLF and both overall and organ-specific cancers risks in MetS populations [44]. Consistent with this evidence base, our study found no association between HLF adherence and breast cancer risk reduction in women

with MetS. However, within the MetS subgroup, HLF protective effects against overall cancer risk were exclusively observed in men, with no detectable association in women. We further conducted a separate analysis of site-specific cancers to clarify their association with HLF. Our findings revealed metabolic status dependency in the inverse associations between HLF adherence and reduced cancer risk. A healthy lifestyle demonstrated generalized protective effects, showing significant risk reduction for overall, oesophagus, stomach, liver, and lung, bronchus, trachea cancers in men, as well as lung, bronchus, trachea cancer in women, irrespective of metabolic status. Intriguingly, we observed that the association between HLF adherence and reduced cancers incident risk demonstrated metabolic state specificity. We exclusively observed significant risk reductions in men without MetS for cancers of the lip, oral cavity, pharynx, colon, rectum, pancreas, kidney, bladder, and lymphoid leukemia, along with analogous protective effects in women without MetS for overall cancer combined with pancreas, and breast cancers, whereas no such protective associations were detected in participants with MetS. Intriguingly, within the aforementioned results, we identified significant interaction effects between HLF adherence and metabolic status for lip, oral cavity, pharynx, colon, rectum, lung, bronchus, trachea, and lymphoid leukaemia cancers in men, whereas in women this interaction was restricted to lung, bronchus, trachea cancer. These findings demonstrate that MetS attenuates the cancer risk-reduction benefits conferred by HLF adherence, thereby necessitating methods to identify individual risks and develop metabolic status-stratified management strategies.

Collectively, our findings and prior evidence not only elucidate the oncogenic effects of metabolic syndrome but also reveal differential protective effects of healthy lifestyles across site-specific cancers and between sexes. These observations provide novel perspectives for cancer risk assessment and offer insights into potential interactions between metabolic dysregulation and lifestyle factors in carcinogenesis. Ultimately, our findings provide actionable evidence for population-level behavioral modifications to reduce lifestyle-attributable cancer risks, thereby supporting global cancer burden mitigation efforts.

Strengths and limitations

To our knowledge, this is the first study to comprehensively investigate the independent and joint associations of MetS and HLF adherence with site-specific cancer risk across 16 cancer types, employing a sex-stratified design to thoroughly characterize sex-specific effects. The major strengths of this study include: the large sample size, the prospective design of the UK Biobank study, and the additional sensitivity analyses for female-specific cancers. However, this study has some limitations. First, some factors, such as sleep, social interactions, and sugar intake, were not included as covariates. Second, some lifestyle factors were self-reported, which may have led to misclassification of lifestyle-related risk levels. Third, these findings may not be generalizable to other racial or ethnic groups due to the limitations of the UK Biobank.

Conclusions

MetS elevates risks for multiple cancers, while adopting a healthy lifestyle reduces risks of oesophagus, stomach, lung, bronchus, trachea and liver cancers in men and lung, bronchus, trachea cancer in women, regardless of metabolic status. However, MetS counteracts lifestyle-mediated protection against specific cancers—including lip, oral cavity, pharynx, colon, rectum, pancreas, kidney, and bladder cancers and lymphoid leukaemia in men, as well as pancreas and breast cancers in women. These findings underscore the necessity to develop metabolic status-stratified management strategies and implement proactive prevention of MetS.

Abbreviations

MetS	Metabolic syndrome
HR	Hazard ratio
95% CI	95% Confidence interval
HLF	Healthy lifestyle factors
TDI	Townsend deprivation index
ICD-10	The International Classification of Diseases, 10th Revision
UK	United Kingdom
BP	Blood pressure
HDL-C	High-density lipoprotein cholesterol
HbA1c	Glycated hemoglobin
FFQ	Food Frequency Questionnaire
MVPA	Moderate to Vigorous Physical Activity
IPAQ	Physical Activity Questionnaire
ACS	American Cancer Society
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Author contributions

FL, WH, HZ (Hanrui Zhu), HZ (Haixiang Zhang), HC and XT analyzed the data. The first draft of the manuscript was written by FL, JL, WH, HC, CY and XT. FL,

WH, XH, XR and XT conceived and designed the work. FL, HZ (Hanrui Zhu), HZ (Haixiang Zhang), JL, WH, BC, CY, XY, and XT contributed to data acquisition. FL, JL, WH, XH, XR, CY and XT contributed to the interpretation of the data. All authors have read and approved the submitted manuscript.

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Data availability
The data used in this study are accessible through the UK Biobank resource. All researchers interested in accessing these datasets can register and submit an application through UK Biobank (www.ukbiobank.ac.uk).

Declarations

Ethics approval and consent to participate
This study received ethical approval from the North West Multi-Centre Research Ethics Committee, ensuring compliance with institutional and national guidelines. All participants provided written informed consent prior to their involvement in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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