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Sex disparity in the association between metabolic-anthropometric phenotypes and risk of obesity-related cancer: a prospective cohort study

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Abstract

Background Sex disparity between metabolic-obesity (defined by body mass index, BMI) phenotypes and obesity-related cancer (ORC) remains unknown. Considering BMI reflecting overall obesity but not fat distribution, we aimed to systematically assess the association of our newly proposed metabolic-anthropometric phenotypes with risk of overall and site-specific ORC by sex.

Methods A total of 141,579 men (mean age: 56.37 years, mean follow-up time: 12.04 years) and 131,047 women (mean age: 56.22 years, mean follow up time: 11.82 years) from the UK Biobank was included, and designated as metabolic-anthropometric phenotypes based on metabolic status (metabolically healthy/unhealthy), BMI (non-obesity/obesity) and body shape (pear/slim/apple/wide). The sex-specific association of different phenotypes with overall and site-specific ORC was assessed by hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression models.

Results We found metabolically unhealthy and/or obesity phenotypes conveyed a higher risk in men than in women for overall ORC and colorectal cancer compared with metabolically healthy non-obesity phenotype ($P_{interaction} < 0.05$). Of note, metabolically healthy obesity phenotype contributed to increased risks of most ORC in men (HRs: 1.58 ~ 2.91), but only correlated with higher risks of endometrial (HR = 1.89, 95% CI: 1.54–2.32) and postmenopausal breast cancers (HR = 1.17, 95% CI: 1.05–1.31) in women. Similarly, even under metabolically healthy, men carrying apple and wide shapes phenotypes (metabolically healthy apple/wide and metabolically healthy non-obesity apple/wide) suffered an increased risk of ORC (mainly colorectal, liver, gastric cardia, and renal cancers, HRs: 1.20 ~ 3.81) in comparison with pear shape or non-obesity pear shape.

Conclusions There was a significant sex disparity between metabolic-anthropometric phenotypes and ORC risk. We advised future ORC prevention and control worth taking body shape and sex disparity into account.

Keywords Metabolic status, Obesity, Body shape, Phenotype, Obesity-related cancer, UK Biobank

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Background

Obesity has become a serious public health threat worldwide. More than 600 million are obese and over 4 million people dying from overweight or obese in 2015 according to the global burden of disease [1]. Elevated body mass index (BMI) increases the risk of non-communicable diseases, such as cancer [2]. According to the International Agency for Research on Cancer, the following 13 cancers are categorized as causally related to obesity: colorectal, liver, pancreatic, gastric cardia, renal, thyroid, ovarian, endometrial, postmenopausal breast and gallbladder cancers, esophageal adenocarcinoma, multiple myeloma, and meningioma [3–5]. The development of these obesity-related cancers (ORC) may be related to metabolic dysfunction caused by obesity, but the etiology remains unclear and further prevention strategies are urgently required.

Metabolic abnormalities vary among obese individuals. Specifically, some obese individuals have been observed not to exhibit metabolic abnormalities. This subtype is referred to as metabolically healthy obesity (MHO) compared to metabolically unhealthy obesity (MUO), which has recently been a concerned topic defined by BMI and metabolic status [6, 7]. Over the years, this metabolic-obesity phenotypes have been extensively explored not only in the cardiovascular field [8–11], but also in the area of cancer [6, 12–17]. Nevertheless, findings of studies examining the association between metabolic-obesity phenotypes and overall or site-specific ORC remain inconclusive [6, 15]. Additionally, BMI reflects overall obesity but cannot indicate fat distribution [18–21]. The traditional anthropometric indices used to represent body shape, i.e., waist and hip circumferences, may produce biased risk estimates when combined with BMI due to the influence by the strong association between BMI and cancer [22]. Previous studies have proposed to apply the allometric anthropometric body shape indices independent of BMI, i.e., a body shape index (ABSI) and hip index (HI), to measure body shape. We herein constructed "metabolic-body shape phenotypes" using metabolic status and body shape defined by ABSI and HI. Notably, the deposition of adipose tissue varies by sex [23–26]. There are also sex differences in the association of BMI and ABSI-HI with the risk of colorectal cancer [4, 27–29]. However, only one study examined the relationship between metabolic-obesity phenotypes and ORC by sex, and found MUO phenotype had a higher risk of colon cancer in men than in women [15], let alone the sex disparity in the association between metabolic-body shape phenotypes and ORC.

Therefore, the primary aim of this study was to prospectively assess the sex-specific associations of the metabolic-anthropometric phenotypes based on metabolic status, BMI and ABSI-HI categories with risks of overall and site-specific ORC in the UK Biobank. The results would help to identify individuals that should pay more attention to obesity management, metabolic abnormalities surveillance and body shape control to reduce the burden of future ORC.

Methods

Study design and participants

The UK Biobank is a large prospective study database of 500,000 participants aged 37–73 years recruited between 2006 and 2010 by 22 assessment centers in the United Kingdom (detailed information: https://www.ukbiobank.ac.uk). Information on sociodemographic characteristics, lifestyles, diseases and drug use of study participants was obtained through touch-screen questionnaires and brief oral interviews. Physical measurements and blood assays were also performed to collect physical indices and blood indicators. The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (REC reference for the UK Biobank 11/NW/0382). All participants provided written informed consent and their identity information was kept confidential in the datasets.

In the primary analysis of this study, after excluding participants with cancer diagnosis except for non-melanoma skin cancer at baseline (15,514 men and 28,480 women), BMI ≤ 18.5 kg/m^2, and missing phenotype information and covariates, 141,579 men and 131,047 women were included. The detailed study design and analysis process is shown in Additional file 1: Fig S1.

Definitions of metabolic-anthropometric phenotypes

As shown in Table 1, we classified BMI into obesity (≥ 30 kg/m^2) and non-obesity (< 30 kg/m^2) according to the World Health Organization criteria [30]. Based on National Cholesterol Education Program Adult Treatment Panel-III (NCEP ATP-III) [31] criteria and previous research [32, 33], we used six markers including blood pressure, c-reactive protein, triacylglycerol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and glycated hemoglobin to assess metabolic health status. For the body shape, sex-specific medians of ABSI and HI in the complete dataset of the present study were employed [34, 35]. Subsequently, participants were categorized into four metabolic-obesity phenotypes based on BMI and metabolic status: metabolically healthy non-obesity (MHN), metabolically healthy obesity (MHO), metabolically unhealthy non-obesity (MUN), and metabolically unhealthy obesity (MUO). Similarly, eight groups of metabolic-body shape phenotypes were designated based on the combination of body shape and metabolic health status: metabolically healthy/unhealthy pear (MHP/MUP), metabolically healthy/unhealthy slim

Table 1 Definition of metabolic status, degree of obesity and body shape

	Criteria	Method of calculation
Metabolic		
Healthy	Score ≥ 4	(1) SBP < 130 mmHg and DBP < 85 mmHg and no antihypertensive medications, score1 = 1; (2) CRP < 3 mg/L, score2 = 1; (3) Triacylglycerols < 2.3 mmol/L, score3 = 1; (4) LDL-C < 3 mmol/L and no cholesterol lowering medication, score4 = 1; (5) HDL-C > 1 mmol/L, score5 = 1; (6) HbA1c < 42 mmol/mol and no diabetes medications, score6 = 1; Score = sum (score1-score6)
Unhealthy	0 ≤ Score < 4	
Obesity		
Non-obesity	18.5 ≤ BMI < 30	BMI = Weight (kg) * Height $(m)^{-2}$
Obesity	BMI ≥ 30	
Body shape		
Pear	ABSI ≤ Median $_{(ABSI)}$ & HI > Median $_{(HI)}$	ABSI = WC (mm)*Weight $(kg)^{-2/3}$*Height $(m)^{5/6}$ HI_{women} = HC (cm)*Weight $(kg)^{-0.482}$*Height $(cm)^{0.310}$ HI_{men} = HC (cm)*Weight $(kg)^{-2/5}$*Height $(cm)^{1/5}$ Median $_{(ABSI)}$: 74 for women and 80 for men Median $_{(HI)}$: 64 for women and 49 for men
Slim	ABSI ≤ Median $_{(ABSI)}$ & HI ≤ Median $_{(HI)}$	
Apple	ABSI > Median $_{(ABSI)}$ & HI ≤ Median $_{(HI)}$	
Wide	ABSI > Median $_{(ABSI)}$ & HI > Median $_{(HI)}$	

ABSI A body shape index, *CRP* C-reactive protein, *DBP* Diastolic blood pressure, *HbA1c* Glycated hemoglobin, *HDL-C* High-density lipoprotein cholesterol, *HI* Hip index, *LDL-C* Low-density lipoprotein cholesterol, *SBP* Systolic blood pressure

(MHS/MUS), metabolically healthy/unhealthy apple (MHA/MUA), and metabolically healthy/unhealthy wide (MHW/MUW).

Outcomes

The outcomes were incident overall and site-specific ORC, which was determined utilizing the first cancer record from hospitalization, cancer registries, death registries, and self-reported diseases. We defined ORC using the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes, as well as self-reported information verified by interviewing with a nurse (Additional file 1: Table S1). The follow-up time was calculated from the period of baseline enrollment to the first ORC diagnosis, loss to follow-up, death or end of follow-up (30 September 2021 for England, 31 July 2021 for Scotland, and 28 February 2018 for Wales), whichever occurred first.

Covariates

Sociodemographic characteristics included age, Townsend deprivation index, and ethnicity. Lifestyle factors comprised frequency of alcohol consumption (form daily or almost daily to never), smoking status (never, previous, current), and physical activity level (low, moderate, high). Physical activity levels were evaluated using modified questions from the validated short International Physical Activity Questionnaire (IPAQ), encompassing inquiries about the frequency, intensity, and duration of walking, as well as moderate and vigorous activities [36]. Information on family history of cancer (no, yes) was collected from the touchscreen questionnaire. Women were additionally asked for women reproductive factors (age at menarche, menopausal status, number of live births, number of stillbirths, use of hormone replacement therapy [HRT], and oral contraceptives).

Statistical analysis

The Analysis of Variance (ANOVA) was used to compare continuous variables, which were reported as means (standard deviations). The Chi-square tests were used to compare categorical variables, which were expressed as the quantity (percentage).

The association of metabolic-obesity phenotypes and metabolic-body shape phenotypes with overall and site-specific ORC was assessed using Cox proportional hazards regression models in men and women, respectively. The results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We tested the proportional hazards assumption based on Schoenfeld residuals and no statistically significant deviations were observed. The multivariate models were adjusted for age, Townsend deprivation index, ethnicity, smoking status, alcohol consumption frequency, physical activity level, and family history of cancer. Additional adjustments were made for age at menarche, menopausal status, number of live births, number of stillbirths, use of HRT, oral contraceptive use in analyses restricted to women. We also performed subgroup analyses to assess the associations of these two phenotypes with overall

ORC risk stratified by age (< 60 years, ≥ 60 years), alcohol consumption frequency, smoking status, and physical activity. Furthermore, we examined the sex-specific association between metabolic-obesity phenotypes and ORC risk across the strata of body shape, as well as between metabolic-body shape phenotypes and ORC risk stratified by obese state. We then established metabolic-obesity-body shape phenotypes with the combination of metabolic status, obese state and body shape to examine its relationship with ORC risk in both sexes.

To evaluate the robustness of results, we performed sensitivity analyses. First, we excluded participants who developed ORC or died within 2 years of follow-up and repeated the main analyses. Second, Fine and Gray subdistribution hazards model was used to examine sex-specific associations of the metabolic-anthropometric phenotypes with risks of overall and site-specific ORC.

All analyses were performed using SAS version 9.4 (SAS Institute, USA) and R software (The R Foundation, http://www.r-project.org, version 4.0.2). A level of < 0.05 for bilateral *P* values was considered statistically significant.

Results

Characteristics of the study participants

Among 141,579 men and 131,047 women included in the present study, MHN phenotype accounted for the highest proportion while MHO phenotype for the lowest proportion (Fig. 1A), and the proportion of metabolically unhealthy phenotypes (especially MUN phenotype) was higher in men than in women. On the other hand, the proportion of MHS and MHP phenotypes respectively ranked the largest in men and women, while MUP phenotype constituted the smallest proportion in both sexes (Fig. 1B). All the metabolically healthy-body shape phenotypes took a proportion of more than 75% in women whereas a higher proportion of 41% for the metabolically unhealthy-body shape phenotypes was observed in men. Among both sexes, subjects with MUO and MUW phenotypes were more likely to be older, more deprived, physically inactive, current smokers, non-drinkers, have a family history of cancer, and were more likely to be wide-type when compared to those with MHN and MHP phenotypes, respectively (Additional file 1: Table S2 and S3). During a median follow-up of 12.5 years (interquartile range: 11.8–13.2 years), 5,258 and 8,333 overall ORC cases occurred in men and women, respectively, with the

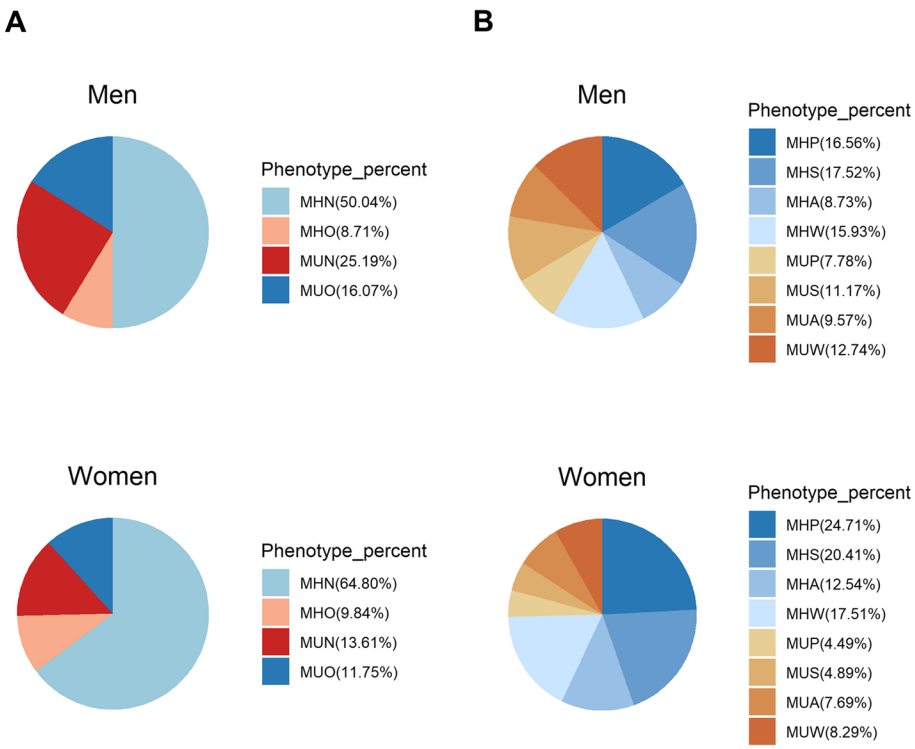

Fig. 1 Proportion of metabolic-obesity/body shape phenotypes in men and women. **A** Proportion of metabolic-obesity phenotypes in men and women. **B** Proportion of metabolic-body shape phenotypes in men and women. Abbreviations: A, apple shape; MH, metabolically healthy; MU, metabolically unhealthy; N, non-obesity; O, obesity; P, pear shape; S, slim shape; W, wide shape

number of site-specific ORC cases shown in Additional file 1: Table S4.

Association between metabolic-obesity phenotypes and ORC

As shown in Table 2, MHO phenotype contributed to an augmented risk of overall ORC in men (HR = 1.36, 95% CI: 1.23–1.50) and women (HR = 1.17, 95% CI: 1.09–1.26) when compared with MHN phenotype. Specifically, increased risks of all ORC types in men (with HRs from 1.58 to 2.91), except colorectal, thyroid cancers and multiple myeloma, were ascribed to MHO phenotype, which, however, only correlated with higher risks of endometrial (HR = 1.89, 95% CI: 1.54–2.32) and postmenopausal

Table 2 Association of metabolic-obesity phenotypes with risk of ORC incidence

		Men				Women			
		MHN	**MHO**	**MUN**	**MUO**	**MHN**	**MHO**	**MUN**	**MUO**
ORC	**Case/total**	2117/70843	508/12330	1486/35651	1147/22755	4655/84919	870/12889	1417/17840	1391/15399
	HR (95%CI)	ref	**1.36 (1.23–1.50)**	**1.22 (1.15–1.31)**	**1.56 (1.45–1.68)**	ref	**1.17 (1.09–1.26)**	**1.09 (1.03–1.16)**	**1.30 (1.22–1.38)**
Colorectal cancer	**Case/total**	1090/70843	216/12330	702/35651	520/22755	966/84919	148/12889	263/17840	243/15399
	HR (95%CI)	ref	1.13 (0.98–1.31)	**1.16 (1.05–1.27)**	**1.42 (1.28–1.59)**	ref	0.99 (0.83–1.18)	1.01 (0.88–1.16)	**1.18 (1.02–1.37)**
Liver cancer	**Case/total**	121/70843	36/12330	125/35651	122/22755	102/84919	18/12889	38/17840	43/15399
	HR (95%CI)	ref	**1.64 (1.13–2.39)**	**1.64 (1.27–2.12)**	**2.66 (2.05–3.45)**	ref	1.07 (0.65–1.78)	1.24 (0.85–1.81)	**1.73 (1.19–2.51)**
Pancreatic cancer	**Case/total**	239/70843	68/12330	175/35651	124/22755	195/84919	41/12889	83/17840	73/15399
	HR (95%CI)	ref	**1.66 (1.27–2.18)**	**1.24 (1.02–1.51)**	**1.53 (1.23–1.91)**	ref	1.37 (0.97–1.92)	**1.42 (1.09–1.84)**	**1.67 (1.26–2.20)**
Esophageal adenocarcinoma	**Case/total**	110/70843	60/12330	107/35651	95/22755	31/84919	7/12889	10/17840	17/15399
	HR (95%CI)	ref	**2.91 (2.12–3.99)**	**1.55 (1.18–2.03)**	**2.18 (1.64–2.89)**	ref	1.45 (0.63–3.32)	**1.08 (0.52–2.22)**	**2.33 (1.25–4.35)**
Gastric cardia cancer	**Case/total**	93/70843	41/12330	101/35651	80/22755	33/84919	7/12889	13/17840	26/15399
	HR (95%CI)	ref	**2.38 (1.64–3.44)**	**1.77 (1.33–2.35)**	**2.24 (1.65–3.04)**	ref	1.20 (0.52–2.73)	1.32 (0.69–2.53)	**2.93 (1.71–5.07)**
Renal cancer	**Case/total**	295/70843	83/12330	215/35651	188/22755	148/84919	32/12889	62/17840	80/15399
	HR (95%CI)	ref	**1.58 (1.24–2.02)**	**1.26 (1.05–1.50)**	**1.79 (1.48–2.16)**	ref	1.24 (0.84–1.83)	**1.42 (1.05–1.92)**	**2.20 (1.65–2.92)**
Multiple myeloma	**Case/total**	205/70843	38/12330	119/35651	67/22755	156/84919	33/12889	39/17840	33/15399
	HR (95%CI)	ref	1.07 (0.75–1.51)	1.04 (0.83–1.31)	0.98 (0.74–1.30)	ref	1.34 (0.92–1.97)	0.88 (0.62–1.27)	0.96 (0.65–1.42)
Thyroid cancer	**Case/total**	39/70843	6/12330	31/35651	14/22755	105/84919	25/12889	26/17840	17/15399
	HR (95%CI)	ref	0.85 (0.36–2.02)	1.45 (0.90–2.36)	1.03 (0.55–1.91)	ref	1.41 (0.90–2.20)	1.13 (0.72–1.76)	0.79 (0.46–1.34)
Ovarian cancer	**Case/total**	/	/	/	/	439/84919	84/12889	92/17840	109/15399
	HR (95%CI)	/	/	/	/	ref	1.26 (0.99–1.60)	0.86 (0.68–1.08)	**1.25 (1.01–1.56)**
Endometrial cancer	**Case/total**	/	/	/	/	406/84919	125/12889	123/17840	251/15399
	HR (95%CI)	/	/	/	/	ref	**1.89 (1.54–2.32)**	1.22 (0.99–1.50)	**2.88 (2.44–3.40)**
Postmenopausal breast cancer	**Case/total**	/	/	/	/	2252/55495	393/8406	726/15558	580/12231
	HR (95%CI)	/	/	/	/	ref	**1.17(1.05–1.31)**	**1.13(1.04–1.23)**	**1.17(1.07–1.29)**

Adjusted for age (continuous), Townsend deprivation index (in quintiles), ethnicity (White, Mixed, Asian, Black, Chinese, other), smoking status (never, previous, current, prefer not to answer), alcohol frequency (daily or almost daily, 3 or 4 times a week, 1 or 2 times a week, 1 to 3 times a month, special occasions only, never), physical activity level (low, moderate, high), family history of cancer (no, yes). Additional adjustments were made for menarche (continuous) menopausal status (no, yes), number of live births (= 0, > 0), number of stillbirths (no, yes), use of HRT (no, yes), oral contraceptive use (no, yes) in women

CI confidence interval, *HR* hazard ration, *MH* metabolically healthy, *MU* metabolically unhealthy, *N* non-obesity, *O* obesity, *ORC* obesity-related cancer

breast cancers (HR = 1.17, 95% CI: 1.05–1.31) in women. Increased risks of most cancers except multiple myeloma and thyroid cancer were observed in men with MUN phenotype and in both sexes with MUO phenotype, respectively. In addition, for overall ORC and colorectal cancer, MHO, MUN and MUO phenotypes conveyed a higher risk in men than in women ($P_{interaction} < 0.05$).

In subgroup analysis (Additional file 1: Table S5), we observed an interaction between age and metabolic-obesity phenotypes in men, which exhibited a greater effect by MHO, MUN and MUO phenotypes on overall ORC risk in < 60 years than that aged 60 years and older ($P_{interaction} < 0.0001$). Besides, among men, there was an interaction between metabolic-obesity phenotypes and body shape in gastric cardia cancer, with the risk effects of MHO/MUO phenotypes more pronounced in pear shape ($P_{interaction} = 0.0102$, Additional file 1: Table S6). In women, we found a more pronounced positive association between MUO phenotype and pancreatic cancer in wide shape ($P_{interaction} = 0.0482$) and between MHO/MUO phenotypes and endometrial cancer in pear and slim shapes ($P_{interaction} = 0.0055$).

Association between metabolic-body shape phenotypes and ORC

In men, for overall ORC, especially colorectal, liver, gastric cardia and renal cancers, apple and wide shapes remained a risk factor even at the healthy metabolic status (MHA and MHW phenotypes, Fig. 2 and Additional file 1: Table S7). This situation was devastated among men with unhealthy metabolic status, where MUA phenotype conveyed the highest risk of esophageal adenocarcinoma and the aforementioned ORC except liver cancer (HR from 1.55 to 3.33), and the highest risk of about threefold for liver cancer was found in MUW phenotype (HR = 2.95, 95%CI: 1.90–4.57) as compared with MHP phenotype. However, in women, metabolically healthy phenotypes almost had little effect on ORC risk, except increased risks of overall ORC and colorectal cancer by MHA phenotype compared with MHP phenotype. Correspondingly, all the metabolically unhealthy phenotypes (MUP, MUS, MUA and MUW phenotypes) were associated with increased risks of overall ORC, especially endometrial cancer.

In subgroup analysis, we observed metabolic-body shape phenotypes except MHS phenotype exerted a more pronounced positive effect on the risk of overall ORC in those aged < 60 years than ≥ 60 years in men ($P_{interaction} < 0.0001$, Additional file 1: Table S8). When stratified by obesity, only non-obese men with MUS and MUA phenotypes had a higher susceptibility to develop esophageal adenocarcinoma and gastric cardia cancer ($P_{interaction} = 0.0041$ and 0.008, Additional file 1: Table S9).

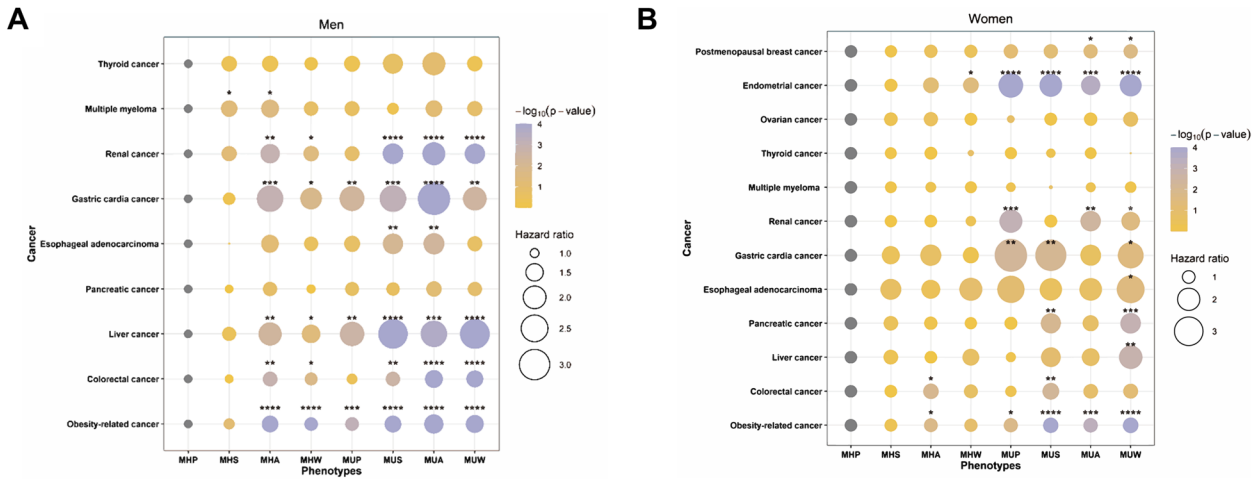

Fig. 2 Association of metabolic-body shape phenotypes with risk of ORC incidence in men (**A**) and women (**B**). The models adjusted for age (continuous), Townsend deprivation index (in quintiles), ethnicity (White, Mixed, Asian, Black, Chinese, other), smoking status (never, previous, current, prefer not to answer), alcohol frequency (daily or almost daily, 3 or 4 times a week, 1 or 2 times a week, 1 to 3 times a month, special occasions only, never), physical activity level (low, moderate, high), family history of cancer (no, yes). Additional adjustments were made for menarche (continuous), menopausal status (no, yes), number of live births (= 0, > 0), number of stillbirths (no, yes), use of HRT (no, yes), oral contraceptive use (no, yes) in women. The color of the bubbles represents the negative logarithm of the *P*-value, while the size of the bubbles indicates the magnitude of the hazard ratio, with larger bubbles representing larger hazard ratios. ****: $P < 0.0001$; ***: $P < 0.001$; **: $P < 0.01$; *: $P < 0.05$. Abbreviations: A, apple shape; MH, metabolically healthy; MU, metabolically unhealthy; ORC, obesity-related cancer; P, pear shape; S, slim shape; W, wide shape

The combined effect of metabolic-obesity-body shape phenotypes on ORC

The proportions of metabolic status, obesity and body shape phenotypes in men and women are showed in Additional file 1: Fig S2. The proportion of MHN-slim (MHNS) and MHN-pear (MHNP) phenotypes was the largest in men and in women, respectively, while MHO-apple (MHOA) phenotype accounted for the smallest share in both sexes. As expected, the proportion of each phenotype with metabolically healthy was higher in women, by contrast to the higher proportion of each phenotype with metabolically unhealthy in men. As shown in Fig. 3, we observed that phenotypes carrying metabolically unhealthy or obesity increased overall ORC risk in both sexes. It was noteworthy that as compared with MHNP phenotype, apple and wide shapes (MHN-apple [MHNA] and MHN-wide [MHNW] phenotypes) increased the risk of ORC, particularly esophageal adenocarcinoma, liver, gastric cardia and renal cancers in men, even under metabolically healthy and non-obese (Fig. 3A and Additional file 1: Table S10). By contrast in women, this situation just occurred in MHNA phenotype, which was positively associated with risk of colorectal cancer (HR = 1.26, 95% CI: 1.05–1.51). Although MUN phenotype in the metabolic-obesity phenotypes contributed to an increased risk of overall ORC (Table 2), only the wide shape (MUN-wide [MUNW] phenotype) increased the risk of ORC when combined with body shape among women. We also observed all combinations of body shapes with MHO and MUO phenotypes were associated with higher risk of overall women ORC, especially endometrial cancer (Fig. 3B and Additional file 1: Table S11).

Sensitivity analysis

As shown in Additional file 1: Table S12, the main results generally remained consistent after excluding participants who developed ORC or died within two years of follow-up. Similarly, most associations remained robust in Fine & Gray competing models (Additional file 1: Tables S13-16).

Discussion

In this study, although a higher risk of overall ORC was ascribed to MUO phenotype in both sexes, we yet observed a conspicuous sex disparity. Specific, MHO phenotype possessed an adverse effect on the majority of ORC in men but only endometrial and postmenopausal breast cancers in women. Additionally, the risk effects of metabolic-obesity phenotypes on ORC were not modified by body shape in men, but in women, MUN phenotype exhibited a dangerous effect only when combined with wide shape. More importantly, even when metabolically healthy, phenotypes carrying apple and wide shapes (MHA/MHW/MHNA/MHNW) predominantly contributed to an increased risk of ORC (mainly colorectal, liver, gastric cardia, and renal cancers) in men.

The association between metabolic-obesity phenotypes and ORC risk has been reported, but evidence on sex

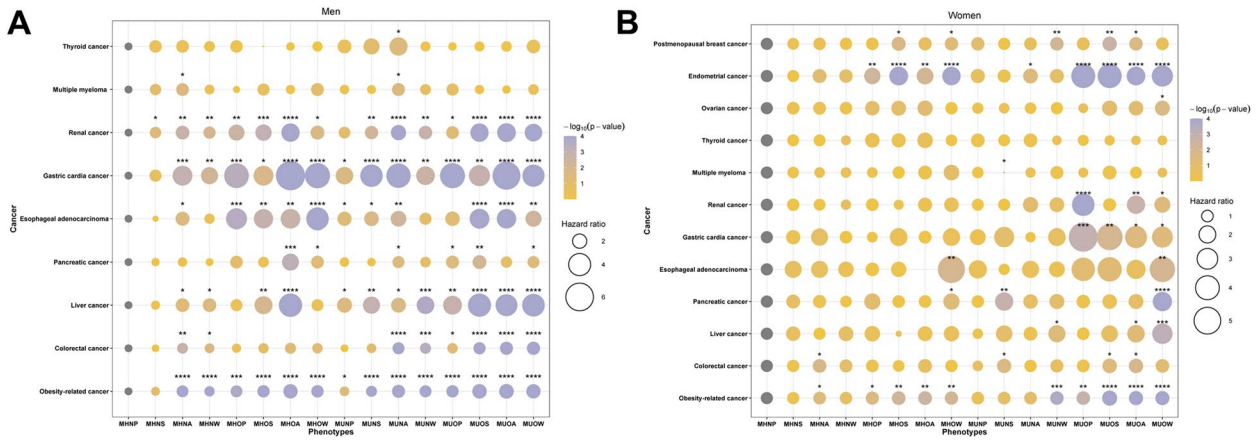

Fig. 3 Association of metabolic-obesity-body shape phenotypes with risk of ORC incidence in men (**A**) and women (**B**). The models adjusted for age (continuous), Townsend deprivation index (in quintiles), ethnicity (White, Mixed, Asian, Black, Chinese, other), smoking status (never, previous, current, prefer not to answer), alcohol frequency (daily or almost daily, 3 or 4 times a week, 1 or 2 times a week, 1 to 3 times a month, special occasions only, never), physical activity level (low, moderate, high), family history of cancer (no, yes). Additional adjustments were made for menarche (continuous), menopausal status (no, yes), number of live births (= 0, > 0), number of stillbirths (no, yes), use of HRT (no, yes), oral contraceptive use (no, yes) in women. The color of the bubbles represents the negative logarithm of the *P*-value, while the size of the bubbles indicates the magnitude of the hazard ratio, with larger bubbles representing larger hazard ratios. ****: $P < 0.0001$; ***: $P < 0.001$; **: $P < 0.01$; *: $P < 0.05$. Abbreviations: A, apple shape; MH, metabolically healthy; MU, metabolically unhealthy; N, non-obesity; O, obesity; ORC, obesity-related cancer; P, pear shape; S, slim shape; W, wide shape

differences was scarce. A prospective study of postmenopausal women from Women's Health Initiative found no significant association between MUN and colorectal cancer risk (HR = 1.65, 95% CI: 0.99–2.74) [37]. Another prospective study from the UK Biobank observed that MHO phenotype was associated with increased risks of endometrial, renal, pancreatic, esophageal, and postmenopausal breast cancers but MUN phenotype was not correlated with ORC [12], without considering sex differences. A recent pooled analysis of 797,193 participants in the Metabolic Syndrome and Cancer (Me-Can) Project 2.0 found MUO was associated with higher relative risks of overall ORC in men and women, especially endometrial, liver and renal cell cancers, but was not associated with multiple myeloma risk in both sexes [15], which was consistent with our study. This pooled study further reported that MUO phenotype was associated with a higher risk of colon cancer in men than in women, which was similar with our results for MHO/MUN/MUO phenotypes with overall ORC and colorectal cancer. Our in-depth study further elucidated MHO phenotype was associated with elevated risks of most ORC in men, but only endometrial and postmenopausal breast cancers in women. Moreover, we observed MUN phenotype was associated with most ORC in men and pancreatic, renal and postmenopausal breast cancers in women. More studies and subjects are needed in the future to confirm these findings of gender differences in the association of metabolic-obesity phenotypes with ORC.

As a measure of general obesity, BMI neither reflects the distribution of fat nor the ratio of fat to lean mass [20]. High BMI and a slim figure may occur simultaneously due to a higher proportion of lean mass. Waist/hip circumferences are closely related to BMI and may lead to biased risk estimates when combining with BMI [19]. Besides, they cannot distinguish subcutaneous fat from visceral fat or lean from fat mass. ABSI and HI, based on the allometric principle used to derive BMI, stand out among the alternative methods for designing a waist/hip index independent of BMI [22]. In analogy to BMI, comparing body mass among individuals with the same height, ABSI and HI, which are related to body volume, compare the transversal body dimensions (waist circumference and hip circumference, respectively) among individuals with the same weight and height. The previous studies found that of all body shapes, apple shape contributed to the highest risk of colorectal cancer in both sexes [35]. To explore the effect of fat distribution on ORC, we combined metabolic status with body shape for the first time to examine its relationship with ORC and to explore whether sex differences similar to the metabolic-obesity phenotypes existed. We found that metabolically healthy phenotypes, especially MHA and MHW phenotypes, were still associated with risk of most ORC among men, but only MHA phenotype contributed to a higher risk of colorectal cancer among women. Notably, the Women's Health Initiative study conducted among postmenopausal women found, with or without adjustment for metabolic status, BMI was not associated with colorectal cancer risk, whereas waist circumference showed an increasing trend [37]. These imply abdominal adiposity may be a potent risk factor for ORC. Differently, a previous UK Biobank study found that central obesity (defined by waist circumference) with metabolically healthy status increased risks of endometrial and postmenopausal breast cancers [12]. It suggests that body shape also plays an important role in ORC risk. While when BMI was used as a measure to define obesity, apple or wide shape was not always included in "obesity". To better investigate the role of metabolic status, obesity, and body shape in ORC, we combined them in our analysis. Apple and wide shapes still increased ORC risk in men even with the presence of metabolically healthy status and non-obesity. Although all body shapes were linked to a higher risk of ORC in men when combined with metabolically unhealthy or obese, MUN phenotype was associated with a higher ORC risk in women only accompanied with wide shape. This hints body shape may provide more value for risk stratification of ORC based on metabolic and obese state in a sex-specific pattern.

There are several strengths in this study. To our knowledge, this was the first study to explore the sex disparity of metabolic-obesity phenotypes with overall and site-specific ORC using the UK Biobank database, of which prospective design and relatively large sample size provided modest statistical power. Second, we combined body shape, defined by ABSI-HI and better reflecting the distribution of adiposity, with metabolic status to explore its relationship with ORC risk for the first time. In addition, we combined metabolic status, obesity and body shape for further risk stratification of high-risk population. A limitation of this study was that other definitions of metabolically (un)healthy status were not considered. For example, some studies defined metabolic status using five criteria including abdominal obesity [6], while others also included insulin sensitivity [38, 39]. In this study, six biomarkers were used to define metabolic status, which was consistent with a UK Biobank study [40]. Additionally, we classified metabolic states based on metabolic indicators at baseline, and shifts across phenotypes might occur throughout follow-up. A recent cardiovascular study found a higher incidence of atherosclerotic cardiovascular disease (ASCVD) in participants who transitioned from MHO to MUO, however MHO-throughout did not increase ASCVD risks [41]. Further consideration of metabolic status changes and ORC risk is needed.

Conclusions

Our study found sex disparity in the relationship between metabolic-anthropometric phenotypes and ORC. Generally, even if metabolically healthy and non-obese, apple- or wide-shape still increased the risk of most ORC in men, but only apple shape was positively associated with colorectal cancer in women. Furthermore, body shape did not modify the risk effects of metabolic-obesity phenotype on ORC in men, but MUN phenotype was a risk factor for ORC in women only combined with wide shape. Therefore, more consideration of body shape and sex disparity was warranted in the risk assessment of ORC, and more attention should be paid to early body shape management to reduce the burden of ORC.

Abbreviations

A	Apple
ABSI	A body shape index
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
HI	Hip index
ICD	International Classification of Diseases
MH	Metabolically healthy
MU	Metabolically unhealthy
N	Non-obesity
O	Obesity
ORC	Obesity-related cancer
P	Pear shape
S	Slim shape
W	Wide shape

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03592-9.

Additional file: Fig S1. Flowchart of the study design. Fig S2. Proportion of metabolic-obesity-body shape phenotypes in men and women. Table S1. Cancer definitions in UK Biobank Study. Table S2. Baseline characteristics of participants according to metabolic-obesity phenotypes in men and women. Table S3. Baseline characteristics of participants according to metabolic-body shape phenotypes in men and women. Table S4. Number of obesity-related cancer (ORC) cases. Table S5. Subgroup analysis of metabolic-obesity phenotypes and ORC. Table S6. Association between metabolic-obesity phenotypes with risk of ORC incidence after stratification by body shape. Table S7. Association between metabolic-body shape phenotypes with risk of ORC incidence. Table S8. Subgroup analysis of metabolic-body shape phenotypes and ORC. Table S9. Association between metabolic-body shape phenotypes with risk of ORC incidence after stratification by obesity. Table S10. Association between metabolic-obesity-body shape phenotypes with risk of ORC incidence in men. Table S11. Association between metabolic-obesity-body shape phenotypes with risk of ORC incidence in women. Table S12. Association between metabolic-anthropometric phenotypes with ORC after excluding those developed ORC or died within 2 years of follow-up. Table S13. Association between metabolic-obesity phenotypes with risk of ORC incidence using Fine & Gray models for competing risk. Table S14. Association between metabolic-body shape phenotypes with risk of ORC incidence using Fine & Gray models for competing risk. Table S15. Association between metabolic-obesity-body shape phenotypes with risk of ORC incidence in men using Fine & Gray models for competing risk. Table S16. Association between metabolic-obesity-body shape phenotypes with risk of ORC incidence in women using Fine & Gray models for competing risk.

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Authors' contributions

Conceptualization: FS; Data Curation: JXG; Formal Analysis: FL, YP and PW; Funding Acquisition: MZ and FS; Project Administration: FS; Software: JXG, CS and XW; Supervision: FS; Validation: HZ, CS and XW; Visualization: JXG, JLG and AQ; Writing—Original Draft: JXG; Writing—Review and Editing: FL YP, PW, CS XW, HZ, JG, AQ, FS. All authors read and approved the final manuscript.

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Availability of data and materials

Data from the UK Biobank are available on application at www.ukbiobank.ac.uk/register-apply.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the North West Multicenter Research Ethics Committee (16/NW/0274) in the United Kingdom. All participants provided written consent to their participation in the UK Biobank.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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