Associations between BMI, polygenic risk score for BMI, lifestyle and the risk of upper gastrointestinal cancer

Yubei Huang
Tianjin Medical University Cancer Institute and Hospital
Zhuowei Feng
Tianjin Medical University Cancer Institute and Hospital
Yuting Ji
Tianjin Medical University Cancer Institute and Hospital
Hongyuan Duan
Tianjin Medical University Cancer Institute and Hospital
Xiaomin Liu
Tianjin Medical University Cancer Institute and Hospital
Yunmeng Zhang
Tianjin Medical University Cancer Institute and Hospital
Yu Zhang
Tianjin Medical University Cancer Institute and Hospital
Zeyu Fan
Tianjin Medical University Cancer Institute and Hospital
Ya Liu
Tianjin Medical University Cancer Institute and Hospital
Ben Liu
Tianjin Medical University Cancer Institute and Hospital
Zhangyan Lyu
Tianjin Medical University Cancer Institute and Hospital
Fangfang Song
Tianjin Medical University Cancer Institute and Hospital
Kexin Chen
Tianjin Medical University Cancer Institute and Hospital
Fengju Song (songfengju@163.com)
Tianjin Medical University Cancer Institute and Hospital

Research Article

Keywords: BMI, PRS, Lifestyle, Upper gastrointestinal cancer, Joint associations

Posted Date: December 13th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3671423/v1

Additional Declarations: No competing interests reported.

Abstract

Objective

To investigate the risk of upper gastrointestinal (UG) cancer associated with BMI across different polygenic risk score for BMI (PRS_{BMI}), and to investigate whether healthy lifestyles could attenuate this risk.

Methods

The joint association between BMI and PRS_{BMI} [low risk: quintile 1–2; intermediate risk: quintile 3–4; high risk: quintile 5] on UG cancer risk were evaluated among 386,427 participants from the UK Biobank cohort, and stratified associations were further investigated according to the scores of lifestyle [favorable lifestyle: 0–1 score; intermediate lifestyle: 2–3 scores; unfavorable lifestyle: 4 scores].

Results

UG cancer significantly associated with BMI, PRS_{BMI}, and numbers of unfavorable lifestyles in dose-response manners, and the adjusted hazard ratios [HRs(95%CI)] were 1.12(0.99–1.27) and 1.39(1.21–1.60) for intermediate and high BMI, 1.15(1.02–1.29) and 1.20(1.05–1.38) for intermediate and high PRS_{BMI}, and 1.40(1.22–1.60) and 2.17(1.79–2.64) for intermediate and unfavorable lifestyles, respectively. Moreover, higher risk was observed for high BMI but low PRS_{BMI} than high PRS_{BMI} but low BMI. After stratifying by lifestyle, there was no obvious interaction and joint association of BMI and PRS_{BMI} with UG cancer risk among participants with favorable lifestyle, while intermediate and unfavorable lifestyle further increased the risk, with HRs ranging from 1.37 to 4.95.

Conclusions

Generally, both high BMI and PRS_{BMI} were associated with increased risk of UG cancer. Moreover, favorable lifestyle could attenuate the increased UG cancer risks associated with high BMI and/or high genetic predisposition of excess BMI. Adopting healthy lifestyles and keeping healthy weight are recommended to reduce UG cancer risk.

INTRODUCTION

Cancer is the leading cause of death and an important burden of disease affecting human health worldwide. According to the cancer statistics report of 185 countries worldwide in 2020 [1], a total of 19.3 million new cancer cases and 10 million cancer deaths occurred in 2020. Gastric cancer (GC) and esophageal cancer (EC) are two common upper gastrointestinal cancers (UG) worldwide, and both of them are leading causes of cancer-related deaths worldwide [1]. Although GC and EC are different cancers at two anatomical sites, they not only had connected anatomical locations, but also had many shared features[2], including shared risk factors [tobacco use, alcohol use, dietary risks, insufficient physical activity, and high body mass index (BMI)][3–7], shared susceptibility locus[2, 8], and shared endoscopic screening modality[9, 10]. Responding to the increasing joint burden of GC and EC is one of the major public health problems faced by several countries today, and optimizing primary and secondary prevention measures are highly and urgently recommended for controlling these malignancies, especially for Eastern Asia countries [1, 6, 7].

Among the shared risk factors between GC and EC, BMI has been the focus of research. Most previous evidence based on large sample size and prospective cohort studies showed virtually consistent and significant association between BMI and risks of GC and EC, though the strength of associations varied across different population and differed between GC, EC, and subtypes[11–15]. Moreover, mendelian randomization (MR) study also supported that genetically determined BMI with single-

nucleotide polymorphisms (SNPs) from genome-wide association study (GWAS) had a causal role in increasing risk of UG cancer [16, 17]. Although several factors could contribute to the inconsistent strength of the association between BMI and UG cancer in different populations [11–15], genetic heterogeneity would be one of the key factors for this inconsistency. Analyses of joint association of the actual BMI and genetically predicted BMI measured by polygenic risk score (PRS_{BMI}) may reflect the interaction of environment and genetic factors with UG cancer [18]. However, few studies had investigated the joint association of actual BMI and PRS_{BMI} with risk of UG cancer. Additionally, previous studies also suggested that healthy lifestyles could attenuate the UG cancer risk [19], and fewer studies explored whether adherence to healthy lifestyles could attenuate the increased risk of UG cancer under the joint interaction between actual BMI and PRS_{BMI}.

Therefore, based on the UK Biobank cohort, we aimed to investigate the independent and joint association of BMI and PRS_{BMI} with the risk of UG cancer, then to investigate whether theses associations could be modified by comprehensive unhealthy lifestyles based on four common lifestyle factors [smoking, alcohol consumption, unhealthy diet, and no regular physical activity], thereby providing potential suggestions for UG cancer prevention.

METHODS

Study population

UK Biobank (https://www.ukbiobank.ac.uk/) is a large prospective cohort study with open access for public health research. Details of study design and recruitment have been described previously [20]. Briefly, all participants were registered with the UK National Health Service (NHS) and lived within 40 km of one of the UK Biobank assessment centers. Approximately 9.2 million people were initially invited to participate. Overall, the UK Biobank finally recruited 502,419 participants aged 40 to 69 years between 2006 and 2010 from 22 assessment centers throughout England, Scotland, and Wales, with a participation rate of 5.5% [20]. After informed consent, a self-administered, touch-screen questionnaire and face-to-face interviews were provided for all participants to collect detailed baseline information, including sociodemographic characteristics, early-life factors, health and medical history, sex-specific factors, and so on. Moreover, blood, urine and saliva samples were collected [21], and health conditions were regularly followed up to better understand the processes over a wide range of complex diseases and improve public health. Participants who lived within a 35 km radius were invited to attend a repeat assessment clinic at the UK Biobank Coordinating Centre in Stockport between August 2012 and June 2013. Repeat assessments were completed in 20 000 participants (9000 men) with a response rate of 21%.

In this study, a total of 386,427 eligible participants were included in the finally analyses after excluding 34,607 participants with previous cancer, 2,920 participants without baseline BMI, 13,687 participants without PRS for BMI, and 64,778 participants with other cancer at the end of follow-up (**Fig.S1**). The UK Biobank study was approved by the National Health Service National Research Ethics Service, and all participants provided written informed consent. Moreover, the present study was conducted followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [22].

Exposure Assessment

The primary analysis variables in this study were BMI, standard PRS for BMI, and lifestyle. Weight and height were measured at the assessment center. Standing height was measured by a Seca 202 stadiometer. Body weight was measured by the Tanita BC-418 MA body composition analyzer, accurate to the nearest 0.1 kg. BMI was calculated as weight in kilograms divided by height in meters squared, and were divided into five groups according to the quintiles of BMI: quintile 1 (Q1): $\leq$23.51 kg/m^2; Q2: 23.52–25.66 kg/m^2; Q3: 25.67–27.80 kg/m^2; Q4: 27.81–30.78 kg/m^2; and Q5: $\geq$30.79kg/m^2 [23].

Two sets of PRS scores for 53 disease and quantitative traits were available in the UK Biobank data based on the genomic data, including the standard PRS set and the enhanced PRS set. The two sets of PRS were calculated with a Bayesian approach to estimate non-zero weights for multiple diseases for the same individual in ~ 6M SNPs spread throughout the genome, and these scores were approximately centered on zero across all ancestries [24]. The enhanced PRS set only covered

21% of the individuals in the UK Biobank cohort, and standard PRS set covered all individuals of the cohort. Therefore, the standard PRS set was used in this study. The standard PRS was further reclassified into five groups based on the quintiles of PRS_{BMI}, with Q1: < -1.02; Q2: -1.02, -0.45; Q3: -0.44, 0.05; Q4: 0.06, 0.62; and Q5: ≥ 0.63 [23].

Lifestyle composite scores were assessed based on four lifestyle factors, including smoking, alcohol drinking, physical activity and diet. For smoking status, a score of 1 was assigned to current or former smoker and 0 to never smoker. For alcohol drinking, a score of 1 was assigned to current or former drinker and 0 to never drinker. For physical activity, a score of 1 was assigned to no regular physical activity and 0 to regular physical activity. According to the World Cancer Research Fund/American Institute of Cancer Research (WCF/AICR) recommendations [25], regular physical activity was defined as at least 75 minutes of vigorous activity per week, 150 minutes of moderate activity per week, vigorous activity once per week, or at least 5 days of moderate activity per week [26]. For diet, total healthy diet score was evaluated based on 7 dietary recommendations from the WCF/AICR, including cooked/ salad/raw vegetable ≥ 3 per day, fresh/dried fruits ≥ 3 per day, oily/non-oily fish ≥ 2 per week, processed meat (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets) < 1 per week, unprocessed red meat (beef/lamb/pork/poultry) < 1 per week, whole grains ≥ 7 per week, and refined grains < 1 per week [25]. If any dietary recommendation was not met, a score of 1 was assigned. To simplify the diet score, total healthy diet scores were further reclassified into healthy diet (≥ 7 scores) and unhealthy diet (< 7 scores) according to the median score [23]. Therefore, a score of 1 was assigned to comprehensive unhealthy diet and 0 to healthy diet. Finally, based on the above 4 factors, the comprehensive lifestyle scores ranged from 0 to 4.

The covariates initially included age, gender, race, average total household income before tax, qualification education, diabetes history, and family history of cancer, which were defined based on either physician diagnosis or self-reported medical conditions.

Primary Outcome

To obtain a relatively stable association between BMI and UG cancer and provide uniform recommendations for the joint prevention of GC and EC, we combined incident GC and EC as the joint primary outcome, namely incident UG cancer during follow-up period. We further performed sensitivity analyses to investigate whether the associations of BMI with GC and EC were relative consistent. Cancer registration data were provided via record linkage to the NHS Central Register and obtained via NHS Digital and recoded according to the International Classification of Diseases Tenth revision code [ICD-10]. Death data for England and Wales were obtained from the death certificates in the NHS Digital and for Scotland by the Information and Statistics Division. At the time of analysis in this study, the full follow-up was updated to 29 February 2020 in England, 28 February 2018 in Wales, and 31 January 2021 in Scotland. Therefore, the endpoint was censored at the first diagnosis of UG cancer, the end dates of follow-up, or the date of death, whichever came first. Person-years were calculated from the date of recruitment to the dates of the first UG cancer diagnosis, death or censoring date, whichever occurred first.

Statistical Analysis

Chi-square tests were used to compare the distribution of baseline categorical variables between cases and non-cases. Linear regression of BMI with PRS_{BMI} was used to investigate the relationship between actual BMI and genetically predicted BMI, and to preliminarily estimate the percentage of actual BMI variance which could be explained by genetically predicted BMI. Bar graph based on percent of participants in quintiles (Q1, Q2, Q3, Q4, and Q5) of BMI by PRS_{BMI} was used to visualize whether there was a separation between actual BMI phenotype and genetically predicted BMI.

To present whether there was a linear or nonlinear relationship between BMI, PRS_{BMI}, lifestyle and UG cancer risk, the dot-line plots with quintiles-based five categories were used to visualize the dose-response relationship of UG cancer risk with index variables. To further simplify the association and allow for easy-to-use recommendations for cancer prevention, both BMI and PRS_{BMI} were further reclassified into three risk groups: Q1- Q2; intermediate risk: Q3- Q4; high risk: Q5, while lifestyle was also reclassified into three categories based on lifestyle scores: favorable lifestyle: 0–1 score; intermediate lifestyle: 2–3 scores, and unfavorable lifestyle: 4 scores [23]. K-M curves were used to graph the survival curves and log-rank test was used to

compare within-group difference in the crude incidences of UG cancer. Univariate Cox regression models was used to measure the magnitude of the crude association as hazard ratios and 95% confidence interval [HRs (95%CI)] between index variable and the risk of UG cancer. Multivariable Cox regression models were further conducted to investigate the independent associations of BMI, PRS_{BMI} and lifestyle with UG cancer risk after adjusting all available baseline confounding variables. Restricted cubic splines of BMI and PRS_{BMI} were nested in the multivariable Cox regression models to preliminarily investigate the non-linear relationship of BMI and PRS_{BMI} with UG cancer risk. To compare whether there was a significant difference between quintiles-based BMI classification and WHO recommended BMI classification [six categories: BMI < 18.5, 18.5–24.9, 25- 29.9, 30-34.9, 35-39.9, and ≥ 40; simplified three categories: BMI < 25 (normal/thinness), 25-29.9 (overweight) and > 30 (obesity)], we re-analyzed the association between BMI and UG cancer risk with the WHO classification.

The subgroup analyses were used to explore the stratified association between actual BMI and UG cancer risk by PRS_{BMI}, with the low BMI as the reference group. Additive interaction term based on BMI and PRS_{BMI} was introduced to explore joint association of actual BMI and PRS_{BMI} with risk of UG cancer, and the level of low BMI and low PRS_{BMI} was used as the uniform reference group for the interaction term (9 levels in total). Similar subgroup and interaction analyses were conducted to explore the stratified and joint association between BMI and UG cancer risk by lifestyles. Mediation analysis was further conducted to evaluate the proportion of PRS_{BMI} effects on UG cancer risk mediated through BMI. Additive interaction based on BMI, PRS_{BMI} and lifestyle was further introduced to explore whether adherence to healthy lifestyle could modify the joint associations of actual BMI and PRS_{BMI} with risk of UG cancer, and the level of low BMI, low PRS_{BMI} and favorable lifestyle was used as the uniform reference group for the new interaction term (27 levels in total).

All *P* values were based on two-sided test, statistical significance was set at $P < 0.05$. All statistical analyses were performed with R software (version 4.2.1).

RESULTS

Baseline characteristics

As shown in **Table S1**, higher crude risk of UG cancer was observed among participants with elder age at recruitment, male, lower average household income, lower education, race of Scotland and Wales, history of diabetes, and family history of cancer (all $P < 0.05$). Multivariable Cox regression analyses showed that UG cancer risk was independently and significantly associated age at recruitment, gender, average household income, and history of diabetes, therefore, these factors would be further adjusted as the final covariates in the subsequent multivariable Cox regression analyses. Moreover, **Figure S2a** showed a significant linear relationship between actual BMI and genetically predicted BMI, and PRS_{BMI} can explain nearly 7% of the actual BMI variance. **Figure S2b** showed a relatively obvious separation between actual BMI and genetically predicted BMI. For example, 6.57% of participants with highest PRS for BMI (Q5) had highest actual BMI (Q5) concurrently, while 1.91% of participants with highest PRS for BMI had lowest actual BMI (Q1).

Independent associations of BMI, PRS_{BMI}, and lifestyle with UG cancer risk

During a median follow-up of 11.0 years, a total of 1,522 cases of UG cancer were documented in this cohort. As shown in **Figure S3a**, a significant non-linear relationship was observed between UG cancer risk and BMI, but not for PRS_{BMI}; and stratified non-linear relationship between UG cancer risk and BMI was also observed by quintiles of PRS_{BMI} (**Figure S3b**). When these index variables were reclassified into five categories, increased UG cancer risk significantly associated with BMI, PRS_{BMI} and lifestyle in dose-response patterns, and the crude HRs (95%CI) ranged from 1.22 of quintile 2 to 2.17 of quintile 5 for BMI, 1.02 to 1.35 for PRS_{BMI}, and 1.06 to 3.09 for unhealthy lifestyle (Fig. 1). When these index variables were further simplified into three risk groups, the dose-response relationships were still observed across different risk groups (Fig. 1). Sensitivity analyses show similar crude associations of BMI and PRS_{BMI} with risks of GC and EC (**Figure S4**).

As shown in Table 1, after further adjusting the baseline confounding factors (**Table S1**), adjusted HRs (95%CI) were 1.17 (1.04–1.32) and 1.53 (1.34–1.76) for intermediate and high BMI, 1.19 (1.06–1.33) and 1.29 (1.13–1.48) for intermediate and high PRS_{BMI}, and 1.42 (1.25–1.63) and 2.27 (1.87–2.76) for intermediate and unfavorable lifestyles, respectively. Even after further mutual adjustment, most associations were still significant, with HRs (95%CI) of 1.12 (0.99–1.27) and 1.39 (1.21–1.60) for intermediate and high BMI, 1.15(1.02–1.29) and 1.20(1.05–1.38) for intermediate and high PRS_{BMI}, and 1.40(1.22–1.60) and 2.17(1.79–2.64) for intermediate and unfavorable lifestyle, respectively. Sensitivity analyses show relatively consistent associations of BMI and PRS_{BMI} with risks of GC and EC after adjusting potential confounders (**Table S4**). Re-analyses based on WHO recommended BMI classification showed similar associations based on quintiles-based BMI classification (**Table S2**).

Table 1
Independent associations of BMI, PRS_{BMI}, and lifestyle with UG cancer risk.

Characteristics	Participants	Cases	IR, per	Crude	Adjusted	Adjusted
	N (%)	N (%)	10,000 PYs	HR (95% CI)	HR (95% CI)[1]	HR (95% CI)[2]
BMI (kg/m^2)						
Low BMI	154527(39.99)	436(28.65)	28	Ref.	Ref.	Ref.
Intermediate BMI	154607(40.01)	666(43.76)	43	1.53(1.36–1.73)	1.17(1.04–1.32)	1.12(0.99–1.27)
High BMI	77293(20.00)	420(27.60)	54	1.95(1.70–2.23)	1.53(1.34–1.76)	1.39(1.21–1.60)
PRS for BMI						
Low PRS	154571(40.00)	532(34.95)	34	Ref.	Ref.	Ref.
Intermediate PRS	154570(40.00)	637(41.85)	41	1.20(1.07–1.35)	1.19(1.06–1.33)	1.15(1.02–1.29)
High PRS	77286(20.00)	353(23.19)	46	1.34(1.17–1.53)	1.29(1.13–1.48)	1.20(1.05–1.38)
Lifestyle						
Favorable lifestyle	104732(27.10)	272(17.87)	26	Ref.	Ref.	Ref.
Intermediate lifestyle	259275(67.10)	1081(71.03)	42	1.61(1.41–1.84)	1.42(1.25–1.63)	1.40(1.22–1.60)
Unfavorable lifestyle	22410(5.80)	169(11.10)	75	2.93(2.41–3.55)	2.27(1.87–2.76)	2.17(1.79–2.64)

Note: 1, adjusted age, sex, income, and ever diabetes. Missing data of each variable were coded as another independent category. 2, further adjusted other index variables. BMI: body mass index; PRS_{BMI}/PRS for BMI: polygenic risk score for BMI; UG cancer: upper gastrointestinal cancer; IR: incidence rate; PYs: person-years; HR (95% CI): hazard ratio (95% confidence interval).

Association between BMI on UG cancer risk by PRS_{BMI} or lifestyle

As shown in Table 2, subgroup analyses showed increased risk of UG cancer associated with intermediate [HR (95%CI): 1.33 (1.09–1.62)] and high BMI [HR (95%CI): 1.64 (1.31–2.04)] compared to low BMI within intermediate PRS for BMI, and similar but non-significant association between BMI and UG cancer risk were observed within high PRS_{BMI}. Interaction analyses showed significant joint association of actual BMI and PRS_{BMI} with risk of UG cancer ($P_{interaction}$ = 5.28e-08). More importantly, higher risk of UG cancer was found for high BMI but low PRS_{BMI} compared to high PRS_{BMI} but low BMI, with

HRs(95%CI) of 1.41(1.10–1.80) vs 1.31(1.00-1.71). Mediation analysis showed that 46.5% of PRS_{BMI} effects on UG cancer risk was mediated through BMI (**Figure S5a**). Even after adjusting potential confounders, the proportion of mediation was 34.4% (**Figure S5b**).

Table 2
Association between BMI on UG cancer risk by PRS_{BMI}.

Characteristics	Participants	Cases	IR, per	Stratified association		Joint association		
	N (%)	N (%)	10,000 PYs	Adjusted HR (95% CI) †	*P*	Adjusted HR (95% CI) †	*P*	*P interaction*
Low PRS for BMI	154571(40.00)	532(34.95)	34					
Low BMI	77686(50.26)	216(40.60)	28	Ref.		Ref.		5.28e-08
Intermediate BMI	57975(37.51)	224(42.11)	39	1.06(0.88–1.28)	0.565	1.06(0.88–1.28)	0.555	
High BMI	18910(12.23)	92(17.29)	49	1.41(1.10–1.81)	0.006	1.41(1.10–1.80)	0.006	
Intermediate PRS for BMI	154570(40.00)	637(41.85)	41					
Low BMI	56849(36.78)	151(23.70)	27	Ref.		0.98(0.80–1.21)	0.861	
Intermediate BMI	64744(41.89)	302(47.41)	47	1.33(1.09–1.62)	0.004	1.32(1.11–1.57)	0.002	
High BMI	32977(21.34)	184(28.89)	56	1.64(1.31–2.04)	< 0.001	1.63(1.34–1.99)	< 0.001	
High PRS for BMI	77286(20.00)	353(23.19)	46					
Low BMI	19992(25.87)	69(19.55)	35	Ref.		1.31(1.00-1.71)	0.054	
Intermediate BMI	31888(41.26)	140(39.66)	44	0.98(0.73–1.31)	0.892	1.26(1.02–1.56)	0.035	
High BMI	25406(32.87)	144(40.79)	57	1.29(0.96–1.73)	0.089	1.65(1.33–2.04)	< 0.001	

Note: †, adjusted age, sex, income, and ever diabetes. Missing data of each variable were coded as another independent category. $P_{interaction}$, p value for the additive term based on BMI and PRS_{BMI}. BMI: body mass index; PRS_{BMI}/PRS for BMI: polygenic risk score for BMI; UG cancer: upper gastrointestinal cancer; IR: incidence rate; PYs: person-years; HR (95% CI): hazard ratio (95% confidence interval).

As shown in Table 3, subgroup analyses showed increased risk of UG cancer associated with intermediate and high BMI compared to low BMI within both favorable [HR (95%CI): 1.40 (1.00-1.96)], intermediate [HR (95%CI): 1.46 (1.24–1.71)] and unfavorable [HR (95%CI): 1.49 (0.97–2.30)] lifestyle, but no statistical significance within unfavorable lifestyle. Interaction analyses showed significant joint association of actual BMI and healthy lifestyle with risk of UG cancer ($P_{interaction}$ < 2.20e-16). Moreover, higher risk of UG cancer was observed for unfavorable lifestyle but low BMI compared to high BMI but favorable lifestyle, with HRs(95%CI) of 2.07(1.39–3.07) vs 1.43(1.03–1.98).

Table 3
Association between BMI on UG cancer risk by lifestyle.

Characteristics	Participants	Cases	IR, per	Stratified association		Joint association		
	N (%)	N (%)	10,000 PYs	Adjusted HR (95% CI) †	*P*	Adjusted HR (95% CI) †	*P*	*P interaction*
Favorable lifestyle	104732(27.10)	272(17.87)	26					
Low BMI	48341(46.16)	99(36.40)	20	Ref.		Ref.		< 2.20e-16
Intermediate BMI	39398(37.62)	116(42.65)	29	1.18(0.90–1.55)	0.221	1.16(0.89–1.51)	0.284	
High BMI	16993(16.23)	57(20.96)	34	1.40(1.00-1.96)	0.047	1.43(1.03–1.98)	0.034	
Intermediate lifestyle	259275(67.10)	1081(71.03)	42					
Low BMI	99597(38.41)	304(28.12)	31	Ref.		1.40(1.12–1.76)	0.004	
Intermediate BMI	106047(40.90)	474(43.85))	45	1.11(0.96–1.28)	0.160	1.57(1.26–1.96)	< 0.001	
High BMI	53631(20.69)	303(28.03)	56	1.46(1.24–1.71)	< 0.001	2.06(1.64–2.59)	< 0.001	
Unfavorable lifestyle	22420(5.80)	169(11.10)	75					
Low BMI	6589(29.39)	33(19.53)	50	Ref.		2.07(1.39–3.07)	< 0.001	
Intermediate BMI	9162(40.87)	76(44.97)	83	1.31(0.87–1.98)	0.193	2.64(1.96–3.57)	< 0.001	
High BMI	6669(29.75)	60(35.50)	90	1.49(0.97–2.30)	0.070	2.97(2.15–4.11)	< 0.001	

Note: †, adjusted age, sex, income, and ever diabetes. Missing data of each variable were coded as another independent category. $P_{interaction}$, p value for the additive term based on BMI and PRS_{BMI}. BMI: body mass index; PRS_{BMI}/PRS for BMI: polygenic risk score for BMI; UG cancer: upper gastrointestinal cancer; IR: incidence rate; PYs: person-years; HR (95% CI): hazard ratio (95% confidence interval).

Joint associations of BMI, PRS_{BMI} on UG cancer risk by lifestyle

As shown in Fig. 2 **and Table S3**, after stratifying by lifestyle and adjusting the potential confounding factors, significant joint associations of BMI and PRS_{BMI} with risk of UG cancer could still be observed in intermediate lifestyle, with HRs ranging from 1.41 (95%CI: 1.06–1.88) for low PRS_{BMI} and high BMI to 1.62 (95%CI: 1.26–2.09) for high PRS_{BMI} and high BMI. There was no significantly increased risk of UG cancer associated with the combination of BMI and PRS_{BMI} in either favorable lifestyle or unfavorable lifestyles. Moreover, further interaction analyses based on BMI, PRS_{BMI} and lifestyle showed more obviously joint association of the three index variables with the risk of UG cancer ($P_{interaction}$ = 3.33e-14). Compared to low PRS_{BMI} and low BMI in favorable lifestyle, HRs ranged from 1.37 (1.00-1.88) for low PRS_{BMI} and intermediate BMI in intermediate lifestyle to 4.95 (2.43–10.05) for high PRS_{BMI} and low BMI in unfavorable lifestyle.

Further analyses (**Table S5**) on the joint association between BMI, specific lifestyle and UG cancer risk also supported that specific healthy lifestyle could attenuate the association between BMI and UG cancer, especially for never smoking, followed by regular physical activity. Compared to current or former smokers with low BMI, HRs (95%CI) for never smokers with low and intermediate BMI were 0.56(0.46 to 0.68) and 0.63(0.53–0.76), respectively. Compared to no regular physical activity and low BMI, the increased risk of UG cancer for no regular physical activity and high BMI [HRs (95%CI): 1.54(1.20–1.97)], but decreased to be non-significant for regular physical activity and high BMI.

DISCUSSION

To our knowledge, this is the first study to explore the relationship between BMI and PRS_{BMI} on UG cancer risk, and this is also the first study to explore the joint associations between BMI, PRS_{BMI} and lifestyle on UG cancer risk. Consistent with some previous observational and MR studies [15, 27], this study supported that both high BMI and PRS_{BMI} were associated with increased UG cancer risk. Importantly, BMI seemed to associate with higher UG cancer risk than PRS_{BMI}. Moreover, as the number of unfavorable lifestyle factors increased, such as smoking, alcohol consumption, unhealthy diet, and irregular physical activity, increased risk of UG cancer were observed. Among participants with favorable lifestyle, high BMI, no matter with or without high PRS_{BMI}, would not be associated with increased risk of UG cancer. All of these findings would bring more insights to the prevention of UG cancer.

Based on both quintiles-based BMI classification and WHO recommended BMI classification, the current findings supported that overweight or obesity associated with increased risk of UG cancer. Similar associations were observed for BMI and PRS_{BMI} with risks of GC and EC, respectively, and these were consistent with numerous previous studies [11–15, 17, 28]. Non-linear Cox regression analyses based on restricted cubic splines suggested a U-shaped association between BMI and UG cancer risk, which was similar to previous studies [29]. This special global U-shaped association would probably lead to different subgroup association patterns between BMI and GC, EC, and different subtypes when different subgroup of population was selected. Only when large sample size of population was selected and sophisticated design was used, a relatively stable overall association between BMI and UG cancer risk would be observed. The potential reasons for the increased UG cancer risk associated with low or very low BMI deserved attention. Low or very low BMI could be the results of smoking [29], and it would co-exist with poor health conditions. All of these would lead to increased risk of UG cancer associated with low or very low BMI. More studies are needed to investigate the relationship between extreme BMI (including extreme low or high BMI) and UG cancer risk in the future.

Another important finding was that BMI seemed to be more strongly associated with increased risk of UG cancer than PRS_{BMI}. This finding primarily support that BMI would deserve more attention than genetic predisposition (for BMI) in preventing UG cancer. Moreover, the BMI variance explained by the PRS in TRAILS adolescents was 6.47%[30], and the genome-wide polygenic risk score for BMI accounting for 7.5% of BMI variance based on a clinical cohort of 736,726 adults[31]; both of them were either lower than or similar to the heritability (7%) of BMI reported in this study. We also observed a relatively obvious separation between actual BMI and genetically predicted BMI (**Figure S2**). The potential separation would not only provide valuable insights into both genetic architecture and potential intervention of complex diseases and traits, but also deserve more attention in preventing UG cancer. This may well be one of the reasons why the exposure-outcome association observed in MR studies was relatively lower than that observed in observational studies [17, 32, 33], since MR studies were more likely to yield only a genetic association between exposure and outcome and ignored the interaction between genetic predisposition and other modifiable factors beyond index exposure.

More importantly, as observed in this study, favorable lifestyle could attenuate or even offset the increased risk of UG cancer associated with the interaction between BMI and PRS_{BMI}, while unfavorable lifestyle would further exacerbate the increased risk. Although the combination of PRS_{BMI} and BMI was not associated with increased risk of UG cancer in the favorable lifestyle group (and it was probably due to small sample size), a relatively obvious dose-response pattern of increased UG cancer risk with combination of PRS and BMI deserved attentions in favorable lifestyle. More studies are needed in the future

to validate the current results in the future. Both genetically predicted and actual high BMI are associated with an increased risk of UG cancer, the current results would suggest that lifestyle may play a more important role than BMI and PRS_{BMI}. Until now, although the debate on the contribution of intrinsic and extrinsic risk factors on the cancer development has persisted in the field of cancer etiology exploration [34, 35], interventions based on modifiable factors are still one of the key strategies to reducing cancer burden in the view of public health and cancer prevention. Unhealthy lifestyle factors, such as smoking, alcohol consumption, diet and physical activity, are all modifiable risk factors that directly contribute to the increased risk of UG cancer [19, 26, 36–40]. Moreover, adherence to favorable lifestyle would lead to healthy weight or BMI, which in turn reversed the increased UG cancer risk associated with increased BMI [12, 41–45]. Therefore, integrated interventions to keep a heathy weight and adopt a healthy lifestyle would contribute to a larger reduction of UG cancer incidence.

In addition to the above findings and the strengths based on the prospective cohort design and large sample size, several limitations also deserved attentions. First, PRS used in this study was calculated based on almost all common SNPs throughout the genome rather than selected GWAS-identified SNPs associated with BMI, and it would be unaffordable for resource-limited regions. However, due to its more powerful performance than 81 previously released PRSs and its advantage on predicting genetic predisposition of other multiple diseases for the same individual [24], this standard PRS would be one of the key ways to explore the mechanism of multimorbidity during the post-GWAS era. Second, infection of Helicobacter pylori (HP) was only available in 1–2% of the UK biobank cohort, and detailed information of whether foods were preserved by salting or preservatives was not available in this study. Nevertheless, both lower HP infection rate and lower proportion of UG attributed to HP infection were reported in the European compared to the Asian [46–49], and processed meats (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets) had been incorporated into current dietary scores. Therefore, lack of these information would lead to a relatively limited effect on the current results. Third, the current analysis was not restricted to individuals of European ancestry. According to the principal components analysis of the genotypes in previous study [50], the most common genetic ethnic group (88.26%) of the UK Biobank cohort was British within the broader-level group white ancestry. Therefore, including of the non-European ancestry would inevitably affect the current results. Fourth, due to the potential low incidences of GC and EC in the UK Biobank cohort, we combined them together as the joint UG cancer in this study. Although we observed similar independent associations between BMI and PRS_{BMI} with risks of GC and EC, insufficient data could be used to investigate the subgroup associations by subtypes and the interaction between BMI and PRS_{BMI} on risks of GC and EC, especially the stratified interactions by lifestyles, Further studies with large sample size and sophisticated design are needed to validate the current results in the future.

CONCLUSION

Generally, both high BMI and PRS_{BMI} were associated with increased risk of UG cancer, and the former seemed to more strongly associate with UG cancer risk than the latter. Moreover, favorable lifestyle, including no smoking, no alcohol consumption, healthy diet, and regular physical activity, would attenuate the increased UG cancer risks associated with high BMI and/or high genetic predisposition of excess BMI. Not smoking and regular physical activity were even more noticeable. Therefore, integrated interventions to keep a healthy weight and adopt a healthy lifestyle would be recommended to reduce the UG cancer burden.

Abbreviations

BMI
Body mass index
PRS_{BMI}/PRS for BMI
polygenic risk score for BMI
GC
Gastric cancer
EC

esophageal cancer
UG cancer
upper gastrointestinal cancer
IR
incidence rate
PYs
person-years
HR (95% CI)
hazard ratio (95% confidence interval)

Declarations

Acknowledgements

This research was conducted using the UK Biobank resource under approved project 76092. We thank the investigators and participants in UK Biobank for their contributions to this study. UK Biobank has received ethics approval from the Research Ethics Committee. The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by the above organizations.

Author Contributions

SF, HY, LB and CK were responsible for the design, supervision, and funding of the study. HY, FZ, JY, DH, LX, ZY, ZY, FZ, LY, LB, LZ, SF and CK conducted data sorting, analysis and verification. HY and FZ wrote the complete manuscript. CK, HY and SF provided administrative and material support.

Funding

This work was supported by the National Key R&D Program of China (No. 2021YFC2500400), and National Natural Science Foundation of China (82172894,82073028).

Availability of data and materials

The data are available on application to the UK Biobank trial (https://www.ukbiobank.ac.uk/).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

Department of Epidemiology and Biostatistics, Key Laboratory of Molecular Cancer Epidemiology, Key Laboratory of Prevention and Control of Human Major Diseases, Ministry of Education, National Clinical Research Center for Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin Medical University, Tianjin, 300060, China.

References

1. Sung H, Ferlay J, Siegel RL, Global Cancer Statistics. 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 71 (2021) 209–249.10.3322/caac.21660.
2. Yao L, Yu F, Mao Y, et al. Gastric cancer may share genetic predisposition with esophageal squamous cell carcinoma in Chinese populations. J Hum Genet. 2018;63:1159–68. 10.1038/s10038-018-0501-4.
3. GBD 2019 Cancer Risk Factors Collaborators. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022;400(10352):563–91. 10.1016/S0140-6736(22)01438-6.
4. Chen W, Xia C, Zheng R, et al. Disparities by province, age, and sex in site-specific cancer burden attributable to 23 potentially modifiable risk factors in China: a comparative risk assessment. The Lancet Global Health. 2019;7:e257–69. 10.1016/s2214-109x(18)30488-1.
5. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018;68:31–54. 10.3322/caac.21440.
6. Arnold M, Abnet CC, Neale RE et al. Global Burden of 5 Major Types of Gastrointestinal Cancer. Gastroenterology 159 (2020) 335–349 e15.10.1053/j.gastro.2020.02.068.
7. Lu L, Mullins CS, Schafmayer C, Zeißig S. Linnebacher M.A global assessment of recent trends in gastrointestinal cancer and lifestyle-associated risk factors. Cancer Commun. 2021;41:1137–51. 10.1002/cac2.12220.
8. Abnet CC, Freedman ND, Hu N, et al. A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. Nat Genet. 2010;42:764–7. 10.1038/ng.649.
9. Veitch AM, Uedo N, Yao K. East JE.Optimizing early upper gastrointestinal cancer detection at endoscopy. Nat Reviews Gastroenterol Hepatol. 2015;12:660–7. 10.1038/nrgastro.2015.128.
10. Chen R, Liu Y, Song G, et al. Effectiveness of one-time endoscopic screening programme in prevention of upper gastrointestinal cancer in China: a multicentre population-based cohort study. Gut. 2020. 10.1136/gutjnl-2019-320200.
11. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, International Agency for Research on Cancer Handbook Working Group. Body Fatness and Cancer–Viewpoint of the IARC Working Group. N Engl J Med. 2016;375(8):794–8. 10.1056/NEJMsr1606602.
12. Sung H, Siegel RL, Torre LA, et al. Global patterns in excess body weight and the associated cancer burden. CA Cancer J Clin. 2019;69:88–112. 10.3322/caac.21499.
13. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 2015;16:36–46. 10.1016/s1470-2045(14)71123-4.
14. Pearson-Stuttard J, Zhou B, Kontis V, Bentham J, Gunter MJ. Ezzati M.Worldwide burden of cancer attributable to diabetes and high body-mass index: a comparative risk assessment. The Lancet Diabetes & Endocrinology. 2018;6:e6–e15. 10.1016/s2213-8587(18)30150-5.
15. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ. 2017;356:j477. 10.1136/bmj.j477.
16. Vithayathil M, Carter P, Kar S, Mason AM, Burgess S. Larsson SC.Body size and composition and risk of site-specific cancers in the UK Biobank and large international consortia: A mendelian randomisation study. PLoS Med. 2021;18:e1003706. 10.1371/journal.pmed.1003706.
17. Fang Z, Song M, Lee DH, Giovannucci EL. The Role of Mendelian Randomization Studies in Deciphering the Effect of Obesity on Cancer. J Natl Cancer Inst. 2022;114:361–71. 10.1093/jnci/djab102.
18. Wu S, Zhu W, Thompson P. Hannun YA.Evaluating intrinsic and non-intrinsic cancer risk factors. Nat Commun. 2018;9:3490. 10.1038/s41467-018-05467-z.
19. van den Brandt PA.The impact of a healthy lifestyle on the risk of esophageal and gastric cancer subtypes. Eur J Epidemiol 37 (2022) 931–45.10.1007/s10654-022-00899-w.
20. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. Am J Epidemiol. 2017;186:1026–34. 10.1093/aje/kwx246.

21. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779doi. 10.1371/journal.pmed.1001779.
22. Cho SMJ, Koyama S, Ruan Y, et al. Measured Blood Pressure, Genetically Predicted Blood Pressure, and Cardiovascular Disease Risk in the UK Biobank. JAMA Cardiol. 2022;7:1129–37. 10.1001/jamacardio.2022.3191.
23. Jin G, Lv J, Yang M, et al. Genetic risk, incident gastric cancer, and healthy lifestyle: a meta-analysis of genome-wide association studies and prospective cohort study. Lancet Oncol. 2020;21:1378–86. 10.1016/S1470-2045(20)30460-5.
24. Thompson DJ, Wells D, Selzam S et al. UK Biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits, medRxiv, 2022.
25. Shams-White MM, Brockton NT, Mitrou P, et al. Operationalizing the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Cancer Prevention Recommendations: A Standardized Scoring System. Nutrients. 2019;11. 10.3390/nu11071572.
26. Zhu M, Wang T, Huang Y, et al. Genetic Risk for Overall Cancer and the Benefit of Adherence to a Healthy Lifestyle. Cancer Res. 2021;81:4618–27. 10.1158/0008-5472.CAN-21-0836.
27. Mao Y, Yan C, Lu Q, et al. Genetically predicted high body mass index is associated with increased gastric cancer risk. Eur J Hum Genet. 2017;25:1061–6. 10.1038/ejhg.2017.103.
28. Turati F, Tramacere I, La Vecchia C. Negri E.A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Ann Oncol 24 (2013) 609 – 17.10.1093/annonc/mds244.
29. Recalde M, Davila-Batista V, Diaz Y, et al. Body mass index and waist circumference in relation to the risk of 26 types of cancer: a prospective cohort study of 3.5 million adults in Spain. BMC Med. 2021;19:10. 10.1186/s12916-020-01877-3.
30. Xie T, Wang B, Nolte IM et al. Genetic Risk Scores for Complex Disease Traits in Youth. Circulation: Genomic and Precision Medicine 13 (2020).10.1161/circgen.119.002775.
31. Robinson JR, Carroll RJ, Bastarache L, et al. Quantifying the phenome-wide disease burden of obesity using electronic health records and genomics. Obesity. 2022;30:2477–88. 10.1002/oby.23561.
32. Lin XJ, Wang CP, Liu XD et al. Body mass index and risk of gastric cancer: a meta-analysis. Jpn J Clin Oncol 44 (2014) 783 – 91.10.1093/jjco/hyu082.
33. Thrift AP, Shaheen NJ, Gammon MD, et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. J Natl Cancer Inst. 2014;106. 10.1093/jnci/dju252.
34. Wu S, Powers S, Zhu W. Hannun YA.Substantial contribution of extrinsic risk factors to cancer development. Nature 529 (2016) 43 – 7.10.1038/nature16166.
35. Tomasetti C. Vogelstein B.Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science. 2015;347:78–81. 10.1126/science.1260825.
36. Gonzalez CA, Pera G, Agudo A, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). Int J Cancer. 2003;107:629–34. 10.1002/ijc.11426.
37. Freedman ND, Abnet CC, Leitzmann MF, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol. 2007;165:1424–33. 10.1093/aje/kwm051.
38. Steevens J, Schouten LJ, van den Goldbohm RA. Brandt PA.Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. Gut. 2010;59:39–48. 10.1136/gut.2009.191080.
39. Navarro Silvera SA, Mayne ST, Risch HA, et al. Principal component analysis of dietary and lifestyle patterns in relation to risk of subtypes of esophageal and gastric cancer. Ann Epidemiol. 2011;21:543–50. 10.1016/j.annepidem.2010.11.019.
40. Dong J. Thrift AP.Alcohol, smoking and risk of oesophago-gastric cancer. Best Pract Res Clin Gastroenterol. 2017;31:509–17. 10.1016/j.bpg.2017.09.002.
41. Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017;390:2627–42. 10.1016/S0140-6736(17)32129-3.

42. Qi L. Cho YA.Gene-environment interaction and obesity. Nutr Rev 66 (2008) 684 – 94.10.1111/j.1753-4887.2008.00128.x.
43. Tyrrell J, Wood AR, Ames RM, et al. Gene-obesogenic environment interactions in the UK Biobank study. Int J Epidemiol. 2017;46:559–75. 10.1093/ije/dyw337.
44. Celis-Morales CA, Lyall DM, Bailey MES, et al. The Combination of Physical Activity and Sedentary Behaviors Modifies the Genetic Predisposition to Obesity. Obes (Silver Spring). 2019;27:653–61. 10.1002/oby.22417.
45. Celis-Morales CA, Lyall DM, Petermann F, et al. Do physical activity, commuting mode, cardiorespiratory fitness and sedentary behaviours modify the genetic predisposition to higher BMI? Findings from a UK Biobank study. Int J Obes (Lond). 2019;43:1526–38. 10.1038/s41366-019-0381-5.
46. Ren S, Cai P, Liu Y, et al. Prevalence of Helicobacter pylori infection in China: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2022;37:464–70. 10.1111/jgh.15751.
47. Li M, Sun Y, Yang J, et al. Time trends and other sources of variation in Helicobacter pylori infection in mainland China: A systematic review and meta-analysis. Helicobacter. 2020;25:e12729. 10.1111/hel.12729.
48. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology. 2017;153:420–9. 10.1053/j.gastro.2017.04.022.
49. Eusebi LH, Zagari RM. Bazzoli F.Epidemiology of Helicobacter pylori infection. Helicobacter 19 Suppl. 2014;11–5. 10.1111/hel.12165.
50. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562:203–9. 10.1038/s41586-018-0579-z.

Figures

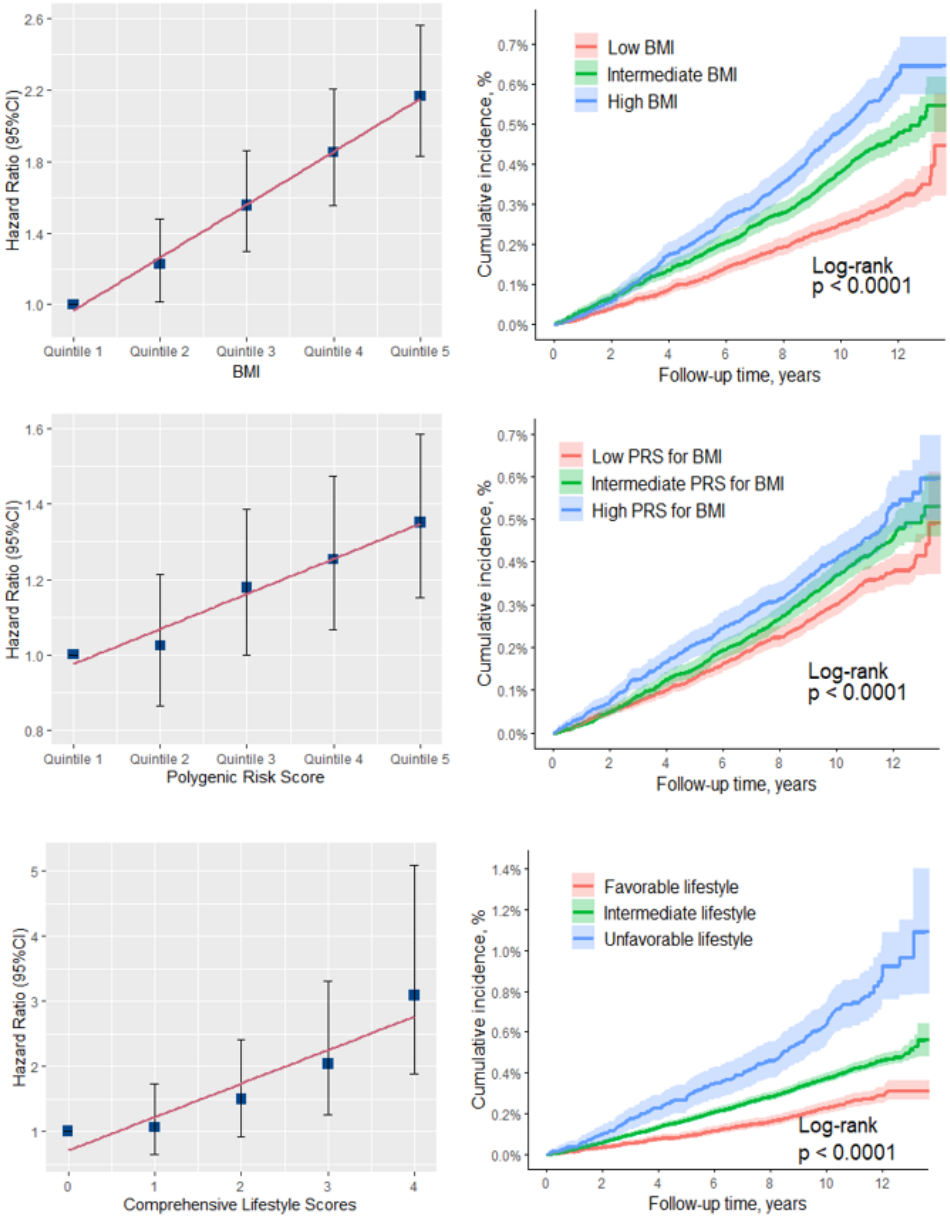

Figure 1

Dot-line plots and K-M curves of BMI, PRS_{BMI}, lifestyle with UG cancer risk

Note: BMI: body mass index; PRS_{BMI}/PRS for BMI: polygenic risk score for BMI; UG cancer: upper gastrointestinal cancer.

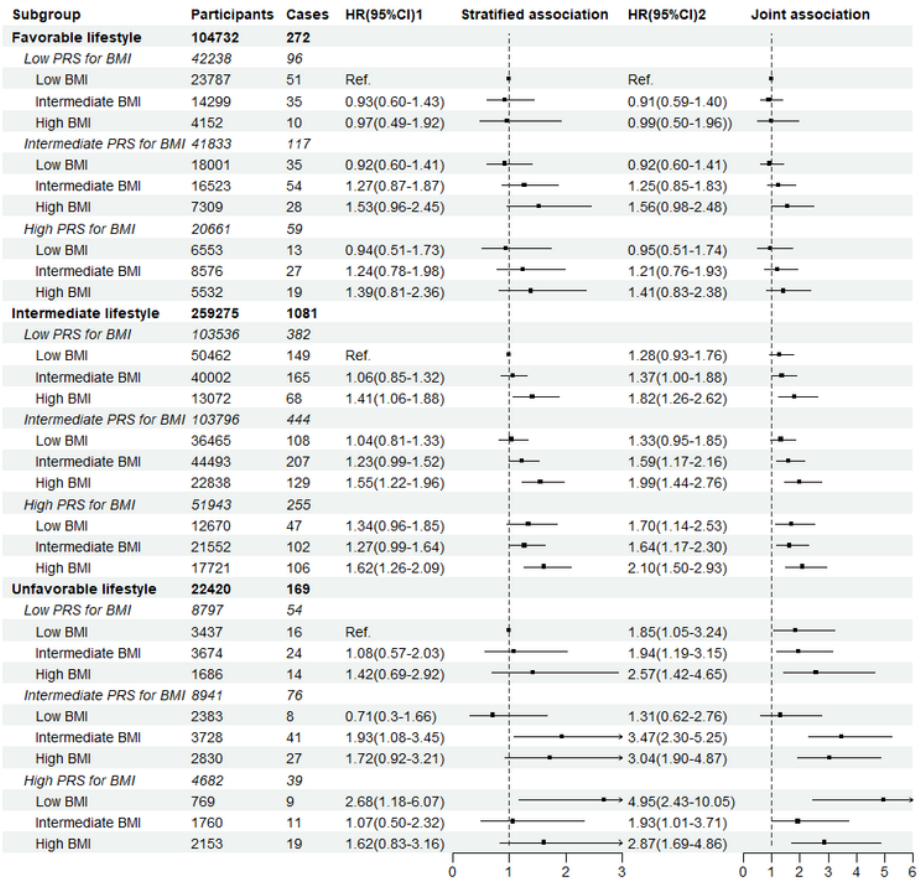

Figure 2

Forest plots of stratified and joint association of BMI, PRS_{BMI} and lifestyle with UG cancer risk

Note: 1, stratified multivariable Cox regression by lifestyle; 2, joint association between BMI, PRS_{BMI} and lifestyle on the risk of UG cancer. Both analyses adjusted age, sex, income, and ever diabetes. Missing data of each variable were coded as another independent category. BMI: body mass index; PRS_{BMI}/PRS for BMI: polygenic risk score for BMI; UG cancer: upper gastrointestinal cancer; HR (95% CI): hazard ratio (95% confidence interval).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx