Preventive Medicine Reports 35 (2023) 102314

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Metabolic risk factors link unhealthy lifestyles to the risk of colorectal polyps in China

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ARTICLE INFO

Keywords:
Colorectal polyps
Unhealthy lifestyles
Metabolic disorders
Mediation effect
Combination effect
Independent effect

ABSTRACT

Colorectal cancer is the second leading cause of global cancer-related deaths, and its precursor lesions are colorectal polyps (CAP). The study aimed to explore the effect of combinations of unhealthy lifestyles on CAP and investigate the mediation role of metabolic disorder in this process. A total of 1299 adults were recruited from a hospital in Jiangsu, China, including 811 cases and 488 adults without diseases. The information on demographic characteristics and lifestyles was collected through questionnaires and the medical record system. Serum biochemical parameters were determined using the automatic biochemical analyzer. Adjusted regression analysis showed that unhealthy lifestyles, including smoking, overnight meals, daily water intake, staying up late, and exercise associated with the risk of CAP. Furthermore, metabolic biomarkers, including BMI, triglycerides, and uric acid, were associated with the risk of CAP. Also, unhealthy lifestyle scores were positively associated with BMI, triglycerides, and CAP. The mediation effect of metabolic biomarkers, such as BMI and triglycerides on the association of unhealthy lifestyle scores with CAP was significant. Available data demonstrate the adverse effect of combinations of unhealthy lifestyle factors on CAP, and metabolic disorders to potentially mediate the association of unhealthy lifestyles with the risk of CAP.

1. Introduction

Colorectal cancer (CRC) is the second leading cause of global cancer-related deaths, and most develop from colorectal polyps (CAP) (He et al., 2018; Heuschmid et al., 2004; Kim et al., 2022). Recently, the prevalence of CAP has been dramatically increasing, and younger(Segev et al., 2020). To date, the etiology of CAP still has not been fully elucidated, but a growing body of evidence showed both metabolic disorders and unhealthy lifestyles contribute to the risk of CAP, including tobacco smoking, alcohol intake, an unhealthy diet, BMI, waist circumference, triglyceride, a high triglyceride to high-density lipoprotein cholesterol and glycosylated hemoglobin percentage, as well as metabolic syndrome (Bailie et al., 2017; Chen et al., 2014; Colussi et al., 2018; Fliss-Isakov et al., 2020; Fliss-Isakov et al., 2018; Fliss-Isakov et al., 2017; Fu et al., 2012; Wallace et al., 2009). In addition, combinations of unhealthy lifestyle factors that interact synergistically could lead to stronger associations with diseases and even mortality(Foster et al., 2018; Loef and Walach, 2012). Most studies have focused on the role of single unhealthy lifestyle factors.

As we all know, unhealthy lifestyles contribute to the risk of metabolic disorders. It means that metabolic disorders could be mitigated by changing unhealthy lifestyles such as physical exercise, a healthy diet, and non-smoking and drinking. For example, a prior study showed that excessive alcohol use behaviors could increase the risk of abdominal obesity, diabetes, and metabolic syndrome (Kim et al., 2011). Poor lifestyle factors, including sedentary time, tobacco smoking, alcohol intake, and dietary intake, were associated with elevated triglyceride levels(Park et al., 2022). However, physical exercise can significantly decrease the risk of metabolic syndrome(Ford et al., 2005). Previous study highlighted the effectiveness of therapeutic lifestyle changes (e.g., atherogenic diet and sedentary lifestyle) in improving metabolic disorders, such as high BMI, triglycerides, low plasma levels of high-density lipoprotein cholesterol, and impaired glucose tolerance(Stone and Saxon, 2005). Also, the incidence of unhealthy lifestyle-related metabolic disorders is rising(Sugimoto et al., 2014). Interestingly, the changes in the prevalence of CAP and unhealthy lifestyle-related metabolic disorders were consistent in recent years(Segev et al., 2020; Sugimoto et al., 2014).

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https://doi.org/10.1016/j.pmedr.2023.102314
Received 11 April 2023; Received in revised form 4 July 2023; Accepted 4 July 2023
Available online 5 July 2023

A growing body of possible mechanisms, such as oxidative stress, inflammation, and insulin resistance, have been found to explain the association between unhealthy lifestyles and CAP(Aggarwal and Gehlot, 2009; Hofstad et al., 1998; Lee et al., 2008; Lee et al., 2007). Up to now, there has been no study that evaluated the mediation role of metabolic risk factors on the association between unhealthy lifestyles and colorectal polyps. Given the close relationship between lifestyles, metabolic changes, and CAP, we predict that the effect of unhealthy lifestyles on CAP might also be affected and mediated through metabolic risk factors. The main aim of the current study was to explore the effect of combinations of unhealthy lifestyle factors and investigate the mediation role of metabolic risk factors in this process by investigating lifestyles and metabolic biomarkers in patients with CAP, informing future public health policy and clinic diagnosis and treatment.

2. Methods

2.1. Study design and population

In the current study, information on 1299 of all 1588 participants (811 of the 1043 cases with colorectal polyps and 488 of the 545 adults without colorectal polyps; 18- to 90- years of age), from 2019 to 2020, was obtained from the medical record system and digestive endoscopy center of a hospital in Jiangsu Province. For the current study, the integrity of medical records and questionnaire information and other diseases, such as cardiac and renal insufficiency, and immune system disease, were considered. The criteria for specific inclusion were as follows: (a) age ≥18; (b) integrity of medical records; (c) integrity of questionnaire information; (d) patients without a family history of CAP; (e) patients without hereditary nonpolyposis colorectal cancer; (f) patients without previous abdominal surgery; (g) patients without other diseases, such as cardiac and renal insufficiency, and immune system disease. The current study met the institution's or the data curator's guidelines for protection of human subjects concerning safety and privacy and was approved by the human ethics committee of the Jiangsu province official hospital in China.

2.2. Questionnaire survey

Questionnaire surveys were completed by a medical doctor, covering basic information (such as age, sex, and birthplace) and lifestyles (including Do you smoke? (yes/no)/How long (years) have you been smoking; Do you drink alcohol? (yes/no)/How long (years) have you been drinking; Do you often eat vegetables? (yes/no)/How often do you eat vegetables per week? (Never, irregularity, <3 days, 3–5 days, >5 days); Do you eat breakfast every day? (yes/no)/Where do you usually have breakfast? (Home, outside, irregularity); Do you have the habit of having late-night snacks? (yes/no); Can you have three meals a day on time? (On time, mostly on time, hardly on time, never); Do you have a habit of overeating? (yes/no); Do you often eat overnight meals? (yes/no), How much (cup) water do you drink each day? (About 250 mL/cup); Do you have the habit of staying up late? (yes/no); How many days a week do you exercise? (Never, <3 days, 3–5 days, >5 days); How long do you exercise each time? (<0.5 h, 0.5–1 h, 1–2 h, >2 h). Is there a known history of intestinal polyps in your immediate family? (yes/no); Is there any known history of cancer in your immediate family? (yes/no). Data from the questionnaire survey could be obtained from the medical record system and digestive endoscopy center of a hospital in Jiangsu Province.

2.3. Medical record and biomarker measurements

Medical record information covers height, weight, waist circumference, and clinical diagnostic results of 811 cases with CAP, including size, location, number, and pathological classification of CAP. Concentrations of serum biochemical parameters, including blood glucose, cholesterol, low-density lipoprotein, triglycerides, and uric acid, were determined using the Automatic Biochemical Analyzer (Japan). For the characterization of metabolic disorders, BMI, blood glucose, cholesterol, low-density lipoprotein, triglycerides, and uric acid, were used as the risk biomarkers of metabolic abnormalities(He et al., 2007; Kanbay et al., 2016; Krauss and Siri, 2004).

2.4. Definitions

Unhealthy lifestyle score, depending on how many of the risk factors the participant had, was used to explore the effect of unhealthy lifestyle scores on a health outcome(Foster et al., 2018). For the current study, an unhealthy lifestyle score was defined as the number of unhealthy lifestyle factors, such as smoking, overnight meals, daily water intake (insufficient), staying up late, and weekly exercise times (<2 days) or duration (<2 h) in the participants.

Furthermore, mediation by metabolic factors was defined as those metabolic factor changes, such as BMI, blood glucose, cholesterol, low-density lipoprotein, triglycerides, and uric acid, mediating the relationship between lifestyle factors and the number of CAP. In the present study, the metabolic disorder was defined as having at least one of the following outcomes: blood glucose ≥6.1 mmol/L, cholesterol ≥5.18 mmol/L, low-density lipoprotein ≥ 3.37 mmol/L, triglycerides ≥1.70 mmol/L or uric acid (male: ≥428 pmol/L; female ≥357 pmol/L).

2.5. Statistical analyses

SPSS23.0, R version 4.1.2, and Graph Pad Prism 6.0 were used in the statistical analysis. As described by a prior study(Cong et al., 2018), for numeric variables, mean values ± standard deviation (SD) were presented for descriptive statistics. An independent-sample *t*-test was performed to analyze differences between groups of normally distributed data. The Mann-Whitney *U* test was performed to compare non-normally distributed data. Confounders based on the prior literature consisted of (a) sources of metabolic changes and risk factors of CAP: smoking, drinking, dietary habits (including regular consumption of vegetables, regular breakfast, late-night snacks, overeating, and overnight meals), water, staying up late, and exercise; (b) causes of metabolic disorder and risk factors of CAP: age, gender, BMI, and history of diseases (including patients without a family history of CAP; patients without hereditary nonpolyposis colorectal cancer; patients without previous abdominal surgery; patients without other diseases, such as cardiac and renal insufficiency, and immune system disease)(Bailie et al., 2017; Chen et al., 2014; Colussi et al., 2018; Fliss-Isakov et al., 2020; Fliss-Isakov et al., 2018; Fliss-Isakov et al., 2017; Ford et al., 2005; Fu et al., 2012; Kim et al., 2011; Park et al., 2022; Stone and Saxon, 2005; Wallace et al., 2009). Spearman's correlation test was used to investigate the correlations between two sets of data. After adjustment for confounding factors, such as age, gender, and BMI, the logistic regression model was performed to explore the association between unhealthy lifestyles and CAP. After adjustment for confounding factors, including age, gender, BMI, waist circumference, diet, smoking, drinking, staying up late, exercise, and history of disease and medication, the logistic regression model was used to investigate the relationship between metabolic risk factors and CAP. Furthermore, the effects of metabolic biomarkers on CAP were explored using the linear regression model, after adjusting age, gender, BMI, waist circumference, diet, smoking, drinking, staying up late, exercise, and history of disease and medication. Finally, mediator analysis based on Preacher and Hayes was performed by adjusting for confounding factors, including age, gender, and BMI. The mediation effects of metabolic risk factors against associations between unhealthy lifestyles and the risk of CAP were examined as previously described (Cong et al., 2021; Cong et al., 2022; Preacher and Hayes, 2008). A *p*-value <0.05 indicated significant.

3. Results

3.1. Descriptive characteristics of study participants

The descriptive characteristics of 1299 participants, including 811 cases with CAP and 488 adults without CAP, are summarized in Table 1. The gender and age distribution of participants show significant differences between the cases with CAP and adults without CAP (both $p < 0.05$). The mean BMI was 26.02 kg/m^2 (SD ± 2.115) in cases with CAP and 24.41 kg/m^2 (SD ± 2.518) in adults without CAP. Furthermore, significant differences between the two groups were also found for lifestyles, including exercise, Smoking, drinking, staying up late, overnight meals, regular breakfast, late-night snacks, and overeating (all $p < 0.05$).

Table 1
Demographic characters of the study population from a hospital in Jiangsu between 2019 and 2020.

Characteristics	CAP group (total = 811) N (%)	Reference group (total = 488) N (%)	χ^2	*P*
Gender				
Male	536 (66.09)	254 (52.05)	25.210	<0.001
Female	275 (33.91)	234 (47.95)		
Age (years)				
18 ~ 44	101 (12.45)	132 (27.05)	60.753	<0.001
45 ~ 59	326 (40.20)	211 (43.24)		
≥60	384 (47.35)	145 (29.71)		
BMI	26.02±2.115	24.41±2.518	11.827	<0.001
Waistline	87.398±6.235	83.084±6.887	11.325	<0.001
Weekly exercise times				
Never	145 (17.88)	17 (3.48)	193.819	<0.001
<3 days	216 (26.64)	61 (12.50)		
3–5 days	388 (47.84)	249 (51.02)		
5–7 days	62 (7.64)	161 (33.00)		
Exercise duration				
<0.5 h	225 (27.74)	24 (4.92)	179.723	<0.001
0.5–1 h	139 (17.14)	74 (15.16)		
1–2 h	413 (50.92)	279 (57.17)		
>2 h	34 (4.20)	111 (22.75)		
Smoking status				
Yes	200 (24.66)	30 (6.15)	71.666	<0.001
No	611 (75.34)	458 (93.85)		
Drinking status				
Yes	176 (21.70)	71 (14.55)	10.121	0.001
No	635 (78.30)	417 (85.45)		
Stay up late				
Yes	219 (27.00)	65 (13.32)	33.396	<0.001
No	592 (73.00)	423 (86.68)		
Overnight meals				
Yes	299 (36.87)	58 (11.89)	95.414	<0.001
No	512 (63.13)	430 (88.11)		
Regular breakfast				
Yes	660 (81.38)	443 (90.78)	21.002	<0.001
No	151 (18.62)	45 (9.22)		
Late-night snacks				
Yes	154 (18.99)	43 (8.81)	24.529	<0.001
No	657 (81.01)	445 (91.19)		
Overeating				
Yes	142 (17.51)	50 (10.25)	12.761	<0.001
No	669 (82.49)	438 (89.75)		

3.2. CAP characteristics of study patients

The CAP characteristics of 811 patients are summarized in Table 2. For the size of CAP, 64.49% was <1 cm, 31.81% was 1–2 cm, and 3.70% was >2 cm. The number of CAP was 1 37.85%, 2 14.80%, and >2 47.35%. Furthermore, the location of CAP was the left colon 61.28%, right colon 20.59%, and total colon 47.35%. For pathological classification of CAP, >50% was a tubular adenoma, and both hyperplastic and serrated polyps were less common (both <1.5%).

Table 2
CAP characters of the study patients (total = 1299; CAP: 811; Reference group: 488) from a hospital in Jiangsu between 2019 and 2020.

Characteristics		N (%)
Size of CAP		
	< 1cm	523 (64.49)
	1 ~ 2cm	258 (31.81)
	> 2cm	30 (3.70)
Number of CAP		
	1	307 (37.85)
	2	120 (14.80)
	> 2	384 (47.35)
Location of CAP		
	Left colon	497 (61.28)
	Right colon	167 (20.59)
	Total colon	147 (18.13)
Pathological classification of CAP		
	Hyperplastic polyp	8 (0.98)
	Inflammatory polyp	90 (11.10)
	Tubular adenoma	464 (57.21)
	Villioustublar adenoma	238 (29.35)
	Serrated polyp	11 (1.36)
BMI (≥25)		
	Reference group	264 (54.10)
	CAP group	679 (83.72)
Blood glucose (≥6.1 mmol/L)		
	Reference group	163 (33.40)
	CAP group	323 (39.83)
Cholesterol (≥5.18 mmol/L)		
	Reference group	53 (10.86)
	CAP group	194 (23.92)
Low-density lipoprotein (≥3.37 mmol/L)		
	Reference group	58 (11.89)
	CAP group	234 (28.85)
Triglycerides (≥1.70 mmol/L)		
	Reference group	36 (7.38)
	CAP group	222 (27.37)
Uric acid (Male ≥428 pmol/L; Female ≥357 pmol/L)	Reference group	125 (25.61)
	CAP group	192 (23.67)
Metabolic disorder		
	Reference group	275 (56.35)
	CAP group	619 (76.33)

3.3. Distribution in metabolic risk factors

The independent sample *t*-test was used to investigate differences in BMI, blood glucose, triglycerides, cholesterol, low-density lipoprotein, and uric acid between cases with CAP and adults without CAP (Fig. 1). BMI, blood glucose, triglycerides, cholesterol, and low-density lipoprotein in patients with CAP was significantly higher than in adults without CAP (all $p < 0.05$). No significant differences were found for uric acid ($p > 0.05$). For different genders, the results of the stratified analysis were consistent with the results of the whole group. Also, the metabolic characteristics of participants showed a higher incidence of metabolic disorders in cases with CAP than adults without CAP (Table 2).

3.4. Association between unhealthy lifestyles and CAP

To understand the associations between unhealthy lifestyles and CAP, after adjustment for age, gender, and BMI, multiple logistic regression models were performed. Table 3 showed that smoking (95 %CI, 4.648–13.029, OR = 7.782), overnight meals (95 %CI, 3.640–8.604, OR = 5.596), and staying up late (95 %CI, 1.559–4.732, OR = 2.717) were positively associated with the risk of CAP. Daily water intake (95 %CI, 0.500–0.663, OR = 0.576) and exercise times (95 %CI, 0.084–0.457, OR = 0.196; reference category: Never) and duration (95 %CI, 0.069–0.360, OR = 0.157; reference category: <0.5 h) were negatively associated with the risk of CAP. In the stratified analysis based on the number of CAP, we also observed similar results (Table 3; Supplemental Tables S1 – S3).

3.5. Association among biochemical parameters and CAP

Table 4 reveals correlations between biochemical parameters and the risk of CAP. Adjusted regression models showed that BMI (95 %CI, 1.024–1.493, OR = 1.237), triglycerides (95 %CI, 1.042–2.160, OR = 1.501), and uric acid (95 %CI, 1.399–3.552, OR = 2.229) was associated with the risk of colorectal polyps, but not blood glucose, cholesterol, and low-density lipoprotein (all $p > 0.05$). For cases with the number of CAP >2, BMI (95 %CI, 1.029–1.576, OR = 1.274), triglycerides (95 %CI, 1.143–2.499, OR = 1.690), and uric acid (95 %CI, 1.643–4.683, OR = 2.774) was positively associated with the risk of CAP. However, no association between metabolic biomarkers and the risk of CAP was found in cases with the number of CAP equal to 2 (all $p > 0.05$). There are similar results in the stratified analysis (Table 4; Supplemental Tables S4 – S6). Furthermore, results showed that blood glucose was statistically associated with CAP with <1 cm (95 %CI, 0.566–0.948, OR = 0.733) (Supplemental Table S6). However, there was no significant association between blood glucose and CAP in other subgroup analyses (all $p > 0.05$).

3.6. Relationships of unhealthy lifestyle scores with metabolic biomarkers and CAP

To investigate the effect of combinations of unhealthy lifestyles on metabolic biomarkers and CAP, a unhealthy lifestyle score(Foster et al., 2018) was used in our current study. The correlations between unhealthy lifestyle scores and metabolic biomarkers were performed using spearman rank correlation (Fig. 2). Results showed that unhealthy lifestyle scores were statistically correlated with BMI ($r_s = 0.201$, $p < 0.01$). However, there were no significant correlations among unhealthy lifestyle scores and blood glucose, triglycerides, cholesterol, low-density lipoprotein, and uric acid (all $p > 0.05$).

After adjustment for age, gender, and BMI, regression analysis was implemented to further investigate the effect of unhealthy lifestyle scores on metabolic biomarkers and CAP (Table 5). Our results showed that unhealthy lifestyle scores were positively associated with BMI [B (95 %CI) = 0.371 (0.254–0.489)], triglycerides [B(95 %CI) = 0.071 (0.035–0.107)], and CAP [B(95 %CI) = 0.297 (0.242–0.351)]. No association between unhealthy lifestyle scores and blood glucose, cholesterol, low-density lipoprotein, and uric acid was found (all $p > 0.05$).

3.7. Mediation analysis

Mediation exists when a predictor could influence a dependent (outcome) variable indirectly via one or more intervening variables (mediators), that could explain the underlying mechanisms between a

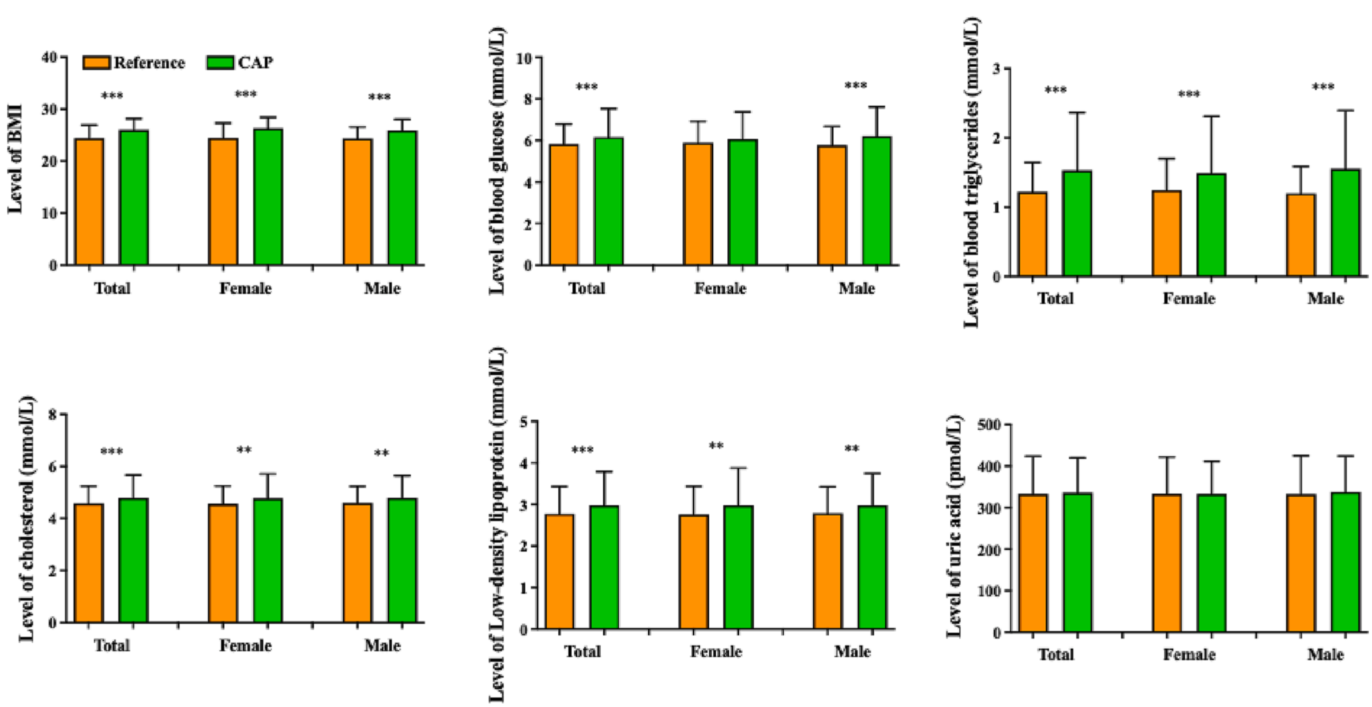

Fig. 1. Distribution of BMI, blood glucose, triglycerides, cholesterol, low-density lipoprotein, and uric acid between cases with CAP and adults without CAP (n = 1299) from a hospital in Jiangsu between 2019 and 2020. ** Significant at $p < 0.01$; *** Significant at $p < 0.001$.

Table 3
The effect of unhealthy lifestyles on CAP (n = 1299) from a hospital in Jiangsu between 2019 and 2020.

	CAP				Number of CAP					
	Yes/No		Yes/No		~1		~2		>2	
	OR [a]	(95 %CI)	OR [b]	(95 %CI)	OR [b]	(95 %CI)	OR [b]	(95 %CI)	OR [b]	(95 %CI)
Smoking	8.097***	4.969–13.193	7.782***	4.648–13.029	8.245***	4.736–14.355	7.827***	3.957–15.483	7.248***	4.100–12.812
Drinking	1.011	0.661–1.545	1.072	0.681–1.686)	1.051	0.637–1.735	1.114	0.590–2.104	1.086	0.649–1.819
Regular consumption of vegetables	1.631*	1.049–2.536	1.670*	1.040–2.681	1.926*	1.115–3.326	1.113	0.579–2.138	1.666	0.964–2.877
Regular breakfast	0.645	0.393–1.058	0.765	0.452–1.292	0.747	0.415–1.345	0.649	0.314–1.339	0.818	0.453–1.478
Late-night snacks	0.598	0.341–1.049	0.491*	0.270–0.893	0.564	0.288–1.102	0.392*	0.167–0.921	0.444*	0.223–0.887
Overeating	1.512	0.935–2.446	1.733*	1.042–2.880	2.176**	1.238–3.825	1.987	0.968–4.081	1.241	0.688–2.238
Overnight meals	7.021***	4.763–10.347	5.596***	3.640–8.604	5.990***	3.725–9.635	6.438***	3.477–11.923	4.882***	2.994–7.963
Water	0.558***	0.489–0.637	0.576***	0.500–0.663	0.570***	0.486–0.670	0.499***	0.403–0.618	0.608***	0.517–0.715
Staying up late	2.428**	1.454–4.055	2.717***	1.559–4.732	2.370**	1.248–4.498	2.465*	1.053–5.770	3.201***	1.673–6.128
Weekly exercise times										
Never	—	—	—	—	—	—	—	—	—	—
<3 days	0.859	0.421–1.752	0.845	0.394–1.814	0.743	0.331–1.669	1.173	0.440–3.125	0.908	0.400–2.061
3–5 days	0.365**	0.181–0.737	0.359**	0.169–0.761	0.291**	0.131–0.648	0.439	0.164–1.175	0.434*	0.193–0.977
5–7 days	0.140***	0.064–0.310	0.196***	0.084–0.457	0.197**	0.079–0.494	0.288*	0.084–0.984	0.164***	0.061–0.443
Exercise duration										
<0.5 h	—	—	—	—	—	—	—	—	—	—
0.5–1 h	0.231***	0.124–0.433	0.252***	0.129–0.493	0.298**	0.143–0.619	0.356*	0.149–0.854	0.184***	0.089–0.382
1–2 h	0.269***	0.147–0.494	0.366**	0.191–0.703	0.380**	0.186–0.776	0.465	0.198–1.090	0.313**	0.155–0.631
>2 h	0.083***	0.038–0.178	0.157***	0.069–0.360	0.182***	0.072–0.462	0.211*	0.057–0.782	0.114***	0.042–0.310

* Significant at $p < 0.05$.
** Significant at $p < 0.01$.
*** Significant at $p < 0.001$.
[a] unadjusted.
[b] adjusted for age, gender, and BMI.

Table 4
The effect of metabolic biomarkers on CAP (n = 1299) from a hospital in Jiangsu between 2019 and 2020.

	CAP				Number of CAP					
	Yes/No		Yes/No		~1		~2		>2	
	OR [a]	(95 %CI)	OR [b]	(95 %CI)	OR [b]	(95 %CI)	OR [b]	(95 %CI)	OR [b]	(95 %CI)
BMI	1.316***	1.246–1.388	1.237*	1.024–1.493	1.220	0.991–1.501	1.139	0.877–1.480	1.274*	1.029–1.576
Blood glucose	1.235***	1.106–1.379	0.984	0.797–1.216	0.733*	0.566–0.948	0.978	0.726–1.317	1.243	0.982–1.573
Triglycerides	1.896***	1.521–2.362	1.501*	1.042–2.160	1.338	0.895–2.000	1.547	0.987–2.426	1.690**	1.143–2.499
Cholesterol	1.105	0.805–1.280	0.916	0.641–1.308	0.939	0.635–1.389	0.798	0.486–1.309	0.925	0.617–1.387
Low-density lipoprotein	1.151	0.905–1.465	0.923	0.612–1.394	0.940	0.593–1.492	0.947	0.527–1.701	0.872	0.545–1.394
Uric Acid	1.330	0.993–1.781	2.229**	1.399–3.552	2.021**	1.213–3.367	1.711	0.898–3.261	2.774***	1.643–4.683

* Significant at $p < 0.05$.
** Significant at $p < 0.01$.
*** Significant at $p < 0.001$.
[a] unadjusted.
[b] adjusted for age, gender, (or) BMI, waist circumference, diet, smoking, drinking, staying up late, exercise, and history of disease and medication.

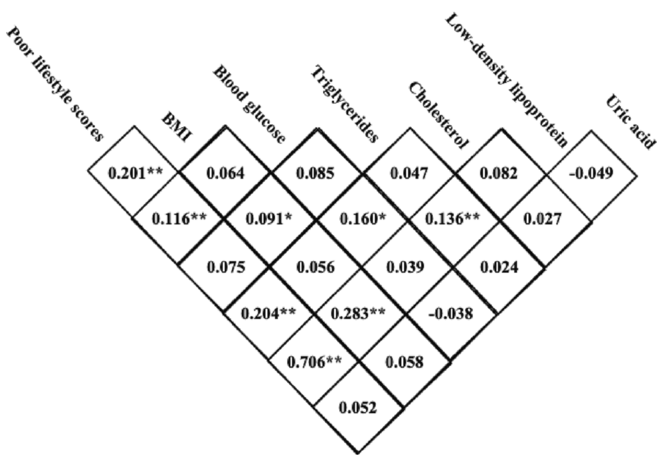

Fig. 2. Spearman rank correlation (r_s) of unhealthy lifestyle scores and metabolic biomarkers, including BMI, blood glucose, triglycerides, cholesterol, low-density lipoprotein, and uric acid from a hospital in Jiangsu between 2019 and 2020. *Significant at $p < 0.05$; ** Significant at $p < 0.01$. n = 1299.

predictor and a dependent variable (Cong et al., 2021; Cong et al., 2022; Preacher and Hayes, 2008). The indirect effect shows the impact of a predictor on a dependent (outcome) variable through mediators. At the same time, the direct effect provides the impact of a predictor on a dependent variable after controlling for mediators. Given that unhealthy lifestyle scores were significantly associated with BMI, triglycerides, and CAP, and CAP was also associated with metabolic biomarker triglycerides and BMI, the subsequent mediation analysis based on Preacher and Hayes was examined (Table 6). Bias corrected 95 Cis shows a significant direct effect [B(95 %CI) = 0.275 (0.221–0.329)], the total indirect effect [B(95 %CI) = 0.063 (0.045–0.083)], and indirect effects through BMI [B(95 %CI) = 0.038 (0.025–0.053)] and triglycerides [B(95 %CI) = 0.025 (0.014–0.036)]. The proportion of BMI and triglycerides-mediated effects in the total effect was 11.21% and 7.31%, respectively.

4. Discussion

The aim of the current study was to explore the effect of combinations of unhealthy lifestyle factors and investigate the mediation role of metabolic risk factors in this process by investigating lifestyles and metabolic biomarkers in patients with CAP. Results showed that unhealthy lifestyles are risk factors for CAP. Similar findings on the

Table 6
Summary of the mediating effect of metabolic biomarkers on the relationship between unhealthy lifestyle scores and CAP from a hospital in Jiangsu between 2019 and 2020.

Model	Product of coefficients		Bootstrapping Bias-corrected 95% CI		Percent of mediated effect
	B	SE	Lower	Upper	
Direct effect	0.275*	0.028	0.221	0.329	/
Indirect effects					
Total	0.063*	0.01	0.045	0.082	18.56
BMI	0.038*	0.007	0.025	0.053	11.21
Triglycerides	0.025*	0.006	0.014	0.036	7.31
Contrasts					
BMI vs. Triglycerides	0.013	0.009	−0.005	0.032	/

* Significant at $p < 0.05$. All regression analyses are controlled for age, gender, and BMI. 5000 bootstrap samples: n = 1299.

Table 5
Relationships of unhealthy lifestyle scores with metabolic biomarkers and CAP (n = 1299) from a hospital in Jiangsu between 2019 and 2020.

	Unhealthy lifestyle scores [a]			Unhealthy lifestyle scores [b]		
	B	95 %CI	P-value	B	95 %CI	P-value
BMI	0.038***	0.272–0.506	<0.001	0.371***	0.254–0.489	<0.001
Blood glucose	0.077*	0.016–0.138	0.014	0.037	−0.008–0.082	0.109
Triglycerides	0.089***	0.053–0.124	<0.001	0.071***	0.035–0.107	<0.001
Cholesterol	0.044*	0.005–0.084	0.029	0.026	−0.015–0.066	0.211
Low-density lipoprotein	0.0.050**	0.012–0.087	0.009	0.033	−0.004–0.071	0.084
Uric Acid	−0.003	−0.024–0.018	0.789	0.000	−0.021–0.020	0.093
CAP	0.375***	0.317–0.433	<0.001	0.297***	0.242–0.351	<0.001

*** Significant at p < 0.001.
[a] unadjusted.
[b] adjusted for age, gender, and BMI.

association between unhealthy lifestyle factors (including smoking, obesity, drinking, and physical activity) and CAP have been previously reported(Bailie et al., 2017; Colussi et al., 2018; Fliss-Isakov et al., 2020; Fliss-Isakov et al., 2018; Fu et al., 2012; Wallace et al., 2009). Also, our study introduced risk factors including overnight meals, daily water intake, and staying up late, which could additionally increase the risk of CAP, and used unhealthy lifestyle scores. To the best of our knowledge, our study is the first to investigate the associations of overnight meals, daily water intake, and staying up late with the risk of CAP and to emphasize the effect of combinations of unhealthy lifestyles.

As we all know, numerous lifestyles are related to a healthy outcome. Improving wider combinations of lifestyles, and recognizing and addressing the determinants of lifestyle are important objectives of public health and individual-level unhealthy lifestyle interventions to avoid increasing inequalities in health(Capewell and Graham, 2010). Combining traditional and emerging factors in extended lifestyle scores could inform future public health policy(Foster et al., 2018). A prior study showed that there could be a stronger association between adverse health outcomes, such as mortality, and combinations of unhealthy lifestyles interact synergistically than single unhealthy lifestyle factors (Loef and Walach, 2012). Furthermore, there could be inconsistent results present in single risk factors with unhealthy health outcomes. One possible explanation could be an interaction between different single lifestyle factors. For example, some participants who smoked might be more physically active or more likely to stay up late in their daily lives. Therefore, it is necessary to explore the effect of combinations of unhealthy lifestyles.

Prior studies showed that possible mechanisms, such as oxidative stress, inflammation, and insulin resistance, have been found to explain the relationship between unhealthy lifestyles and CAP(Aggarwal and Gehlot, 2009; Hofstad et al., 1998; Lee et al., 2008; Lee et al., 2007). However, the underlying mechanisms of the metabolic effect of unhealthy lifestyles on CAP are not well understood. In this study, we characterized the changes in five serum biochemical parameters of metabolic disorders (blood glucose, cholesterol, low-density lipoprotein, triglycerides, and uric acid), and BMI, highlighting for the first time a mediating effect. Results showed that the mediation effect of metabolic biomarkers, such as BMI and triglycerides, on the association of unhealthy lifestyle scores with CAP was significant.

It is clear that the relationship between BMI and triglycerides and CAP is closely related. Evidence of data from 3 prospective studies showed that BMI is strongly associated with serrated polyps(He et al., 2018). Also, Ashktorab et al. found that BMI ≥25 is statistically related to the risk of CAP (OR = 1.64, 95 %CI = 1.14–2.26) in African-Americans (Ashktorab et al., 2014). A prior study found that BMI is a risk factor related to the occurrence of CAP in Chinese people(Yang et al., 2013). Furthermore, previous studies showed significant interactions between BMI and INSR genotypes and between BMI and aspirin with the risk of adenomas(Gunter et al., 2007; Kim et al., 2006). For triglycerides, a recent retrospective study identified that triglycerides are an important risk factor for CAP recurrence after endoscopic resection (OR = 1.76, 95 %CI = 1.00–3.10)(Du et al., 2022). Furthermore, for patients with advanced adenoma, elevated triglycerides could be an independent risk predictor for CAP (OR = 1.55, 95 %CI = 1.02–2.35)(Liu et al., 2020).

The current study has several strengths, including a relatively large sample size, a multitude of lifestyle risk factors, 6 metabolic risk factors, investigating mediation, independent, and combination effect, and using stratified analysis. However, some limitations need to be acknowledged. First, the current study did not use longitudinal follow-up data and was difficult to explore cause-and-effect relationships. Longitudinal follow-up data could further investigate the effect of cessation of unhealthy lifestyles on health outcomes and recognize and address the determinants of lifestyle(Cong et al., 2021). Second, the study did not include the outcome of CRC. Therefore, the outcome of CRC needs to be further evaluated, and whether such mediation and combination effects associated with metabolic risk factors and unhealthy lifestyles remain associated. Last, the study adjusted for some confounding factors but did not exclude other confounding effects from uninvestigated variables, which could affect the accuracy of statistical results. The stratified analysis should further be performed for different levels of confounding factors in the future. Also, we acknowledge some limitations of the questionnaire survey, such as recall bias, and may overestimate unhealthy lifestyles-associated health risks.

5. Conclusion

Overall, our study shows suggestive evidence for the effect of combinations of unhealthy lifestyles on CAP and the mediation role of metabolic risk factors on the association between unhealthy lifestyles and CAP. Results suggest that unhealthy lifestyle scores are positively associated with BMI, triglycerides, and CAP, which is similar to the independent effects. Furthermore, both triglycerides and BMI mediate the association between unhealthy lifestyle scores and CAP. Our current research provides a scientific basis for a further study concerning the effects of both unhealthy lifestyles and metabolic disorders on CAP, especially in combination and mediation effects. In recent years, the prevalence of CAP has been dramatically increasing, and younger. Stronger awareness and public health and individual-level interventions are therefore essential.

CRediT authorship contribution statement

Ning Xu: Methodology, Formal analysis. **Xiaowei Cong:** Conceptualization, Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing. **Rongli Sun:** Methodology, Formal analysis, Writing – review & editing. **Lihong Yin:** Methodology, Writing – review & editing. **Juan Zhang:** Methodology, Writing – review & editing. **Yuepu Pu:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

This work was supported by the Practice Innovation Program of Jiangsu Province, China (KYCX21_0161).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2023.102314.

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