Ther Adv Gastroenterol

2024, Vol. 17: 1–13

DOI: 10.1177/17562848241307601

Mediation role of body mass index in the relationship between food-specific serum immunoglobulin G reactivity and colorectal adenomas in a Chinese population: a cross-sectional study

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Abstract

Background: Colorectal adenomas (CAs) represent a significant global health issue, particularly in China, where lifestyle modifications have contributed to their increased prevalence. These adenomas are precursors to colorectal cancer. While high-fiber diets have been shown to decrease risk, the implications of food-specific serum immunoglobulin G reactivity (FSsIgGR) on CAs remain uncertain and warrant further investigation.

Objectives: To investigate the association between FSsIgGR and the occurrence of CAs in the Chinese population, assess the mediating influence of body mass index (BMI), and offer insights into potential prevention strategies.

Design: A retrospective cross-sectional study.

Methods: This study is based on 8796 individuals who underwent colonoscopy at the Second Medical Center of Chinese PLA General Hospital from 2017 to 2021. We examined the relationship between FSsIgGR and CAs using logistic regression, controlling for various confounders. Interaction effects were explored through subgroup analysis. We addressed missing data using multiple imputation and confirmed the robustness of our findings through sensitivity analysis. The role of BMI as a mediator was quantified using structural equation modeling.

Results: The cohort comprised 2703 patients diagnosed with CAs and 6093 polyp-free controls, with an average age of 50.1 years, of whom 70.1% were male. The analysis revealed a significant inverse association between FSsIgGR and the incidence of CAs (adjusted odds ratio = 0.97; 95% confidence interval: 0.95–0.99; $p < 0.001$). Dose–response analysis indicated a linear reduction in CAs risk correlating with an increased number of IgG-positive food items. Structural equation modeling showed that BMI mediated 6.02% of the effect on CAs risk ($p = 0.038$).

Conclusion: Our findings suggest that FSsIgGR correlates with a reduced risk of developing CAs, with BMI partially mediating this effect. These results add a novel dimension to CAs risk assessment and prevention, highlighting potential dietary interventions.

Keywords: body mass index, Chinese population, colorectal adenomas, cross-sectional study, food-specific serum IgG reactivity, mediation analysis

Received: 3 June 2024; revised manuscript accepted: 29 November 2024.

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Introduction

Colorectal adenomas (CAs) are a significant global health concern, especially in China, due to their potential to evolve into colorectal cancer—the third most prevalent cancer worldwide.[1] Recent epidemiological studies highlight that factors such as aging populations and lifestyle changes, including decreased physical activity and dietary modifications,[2,3] have contributed to an increased prevalence of CAs in China. This rise underscores the imperative for targeted prevention and early detection strategies, emphasizing the crucial role of adenomas in reducing both the incidence and mortality of colorectal cancer.

Dietary factors are paramount in the etiology of CAs. Research indicates that high consumption of red and processed meats is linked to an elevated risk of these lesions,[4] whereas diets rich in fiber, fruits, and vegetables have been shown to mitigate this risk.[5] These dietary elements affect gut health and inflammation,[6] which are vital in the development of CAs. Thus, comprehending the impact of diet on the development of CAs is essential for the formulation of effective dietary guidelines and prevention strategies.

Food-specific serum immunoglobulin G reactivity (FSsIgGR) is an immune response produced by the immune system to specific food antigens, which has been observed in various diseases, including chronic migraine,[7] inflammatory bowel disease,[8] and irritable bowel syndrome,[9] and its test results can provide valuable information for the diagnosis and treatment of these conditions. Currently, many studies both domestically and internationally diagnose food intolerance based on the presence of food-specific IgG antibodies[10,11]; however, this diagnostic method remains controversial. Some research indicates that the detection of food-specific IgG antibodies is not recommended as a diagnostic tool because numerous serum samples exhibit positive IgG4 results without corresponding clinical symptoms.[12] This suggests that the presence of food-specific IgG antibodies should not be considered a causative factor for allergies or intolerance but rather a normal physiological response of the immune system to repeated exposure to food components. Although IgG antibodies are typically considered non-inflammatory, recent studies suggest that persistent activation by specific food antigens can lead to chronic inflammation and alterations in the gut microbiome.[13] This state of chronic inflammation may compromise the integrity of the colorectal mucosa and influence tumorigenic pathways.[14] Nevertheless, the direct impact of FSsIgGR on the development of CAs requires further investigation.

This study explores the negative correlation between FSsIgGR and CAs within a Chinese cohort, focusing on their unique dietary patterns and genetic predispositions, which may affect both FSsIgGR prevalence and CAs development.[15] In addition, the rising incidence of CAs and dietary sensitivities in China underscores the relevance of this research, as it aims to provide insights into the dietary interactions with colorectal tumors. These findings could inform public health policies and personal dietary guidelines.

The primary objective of this investigation is to analyze the relationship between FSsIgGR and the prevalence of CAs in a Chinese population, through the examination of clinical data and food-specific IgG antibody levels. In addition, this study assesses the mediating role of body mass index (BMI), considering the established connections between obesity, dietary habits, and cancer risk.[16] Elucidating BMI's mediating role could offer profound insights into how diet and body composition interact with the risk of CAs.

Materials and methods

Study design and population

This retrospective cross-sectional study aimed to investigate the correlation between FSsIgGR and CAs within the Chinese population. The research was conducted at the Second Medical Center of Chinese PLA General Hospital, covering a period from 2017 to 2021. The study cohort included individuals both outpatients and inpatients presented for routine colonoscopic examinations and voluntarily underwent testing for FSsIgGR. Inclusion criteria were as follows: (1) ages 18–80 years; (2) completion of a colonoscopy with documented data on CAs, taking baseline data from the initial examination if there were multiple records; and (3) completion of testing for 21 types of FSsIgGR. Exclusion criteria included the following: (1) individuals whose polyp pathology did not confirm CAs and (2) individuals who opted out of participating in this study (Figure 1). The study's protocol received approval from the hospital's ethics review committee (approval number

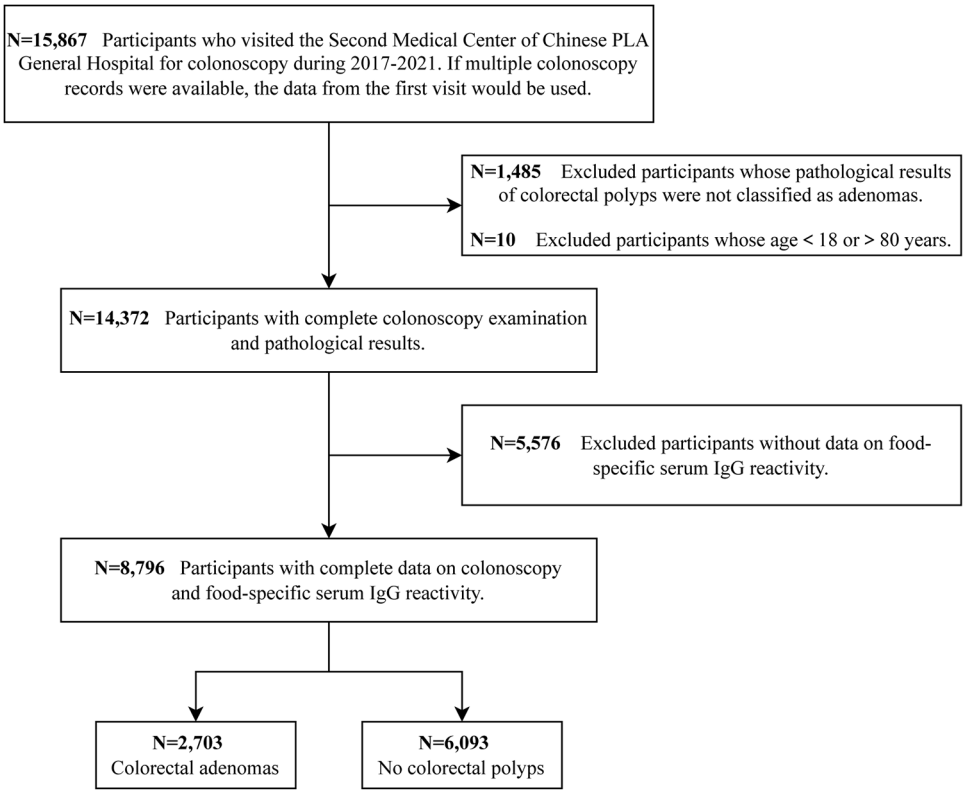

Figure 1. Flow chart of the study population.

S2023-238-02) and conformed to the principles outlined in the Declaration of Helsinki. The reporting of this study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[17]

Definition of FSsIgGR

Participants underwent comprehensive evaluations, and all voluntarily underwent testing for FSsIgGR as part of a broader assessment of gastrointestinal health. FSsIgGR[18,19] was assessed using an enzyme-linked immunosorbent assay. In brief, each participant provided a 2 mL blood sample for the measurement of IgG antibodies against 21 commonly consumed food antigens. These antigens included egg, beer yeast, wheat, milk, garlic, mushroom, tomato, crab, corn, rice, cheese, shrimp, soybean, onion, sesame, cod fish, ginger, pork, chicken, beef, and chili. The IgG levels for each antigen were categorized into four groups: negative (−, <50 U/mL), mildly positive (+, 50–100 U/mL), moderately positive (++, 100–200 U/mL), and severely positive (+++, >200 U/mL), which were assigned numerical scores of 0, 1, 2, and 3, respectively. Based on the count of positive IgG responses, participants were classified into one of three groups: negative (−), single FSsIgGR (SFGR), or multiple FSsIgGR (MFGR).

Definition of CAs

CAs,[20] also known as adenomatous polyps, are benign lesions found on the mucous membrane of the colon or rectum and are recognized as precursors to colorectal cancer. The primary methods for diagnosing CAs are endoscopic examination and histological evaluation. Endoscopic appearance: CAs are generally classified based on their morphology into sessile, flat or slightly elevated, and depressed lesions. Sessile and flat adenomas are less likely to exhibit invasive growth until they reach a larger size. By contrast, depressed lesions may invade the submucosal layer even when they are relatively small. Histological characteristics: histologically, adenomas may show varying degrees of dysplasia, which is defined as the abnormal development and growth of cells within the tissue. The

dysplasia in adenomas can range from low to high grade.

All participants in the study underwent examination by professional gastroenterologists using colonoscopy. If polyps were detected during the examination, any discovered polyps, regardless of quantity, must be sampled and sent to the pathology department for histological evaluation. Based on the pathology results, the CAs were categorized into tubular adenomas, tubulovillous adenomas, villous adenomas, and adenomatous hyperplasia.

Data collection and covariates

The study collected comprehensive data spanning demographic information, medical history, laboratory test results, and results from both FSsIgGR testing and polyp pathology.[21] Demographic information covered age, sex, and BMI. Medical history included family history of colorectal cancer, previous cholecystectomy and appendectomy, presence of fatty liver, diabetes, as well as histories of smoking and alcohol consumption. Laboratory tests included measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γ-GT), creatinine (Cr), uric acid (UA), albumin (ALB), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), neutrophils, lymphocytes, hemoglobin, C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), CA724, and CA125.

Statistical analysis

To assess the normality of the dataset, histogram distributions and the Kolmogorov–Smirnov test were utilized. Continuous variables that adhered to a normal distribution are presented as mean ± standard deviation. Conversely, variables with a skewed distribution are expressed using medians and interquartile ranges. Categorical variables are depicted as proportions and percentages. For the analysis of continuous data, the independent samples Student's *t*-test was employed for normally distributed data, while the Mann–Whitney *U* test was used for data that were not normally distributed. The Chi-square test was utilized for comparing categorical data as necessary.

Logistic regression analysis was conducted to explore the association between FSsIgGR and CAs. FSsIgGR was considered both as a categorical variable (clinical diagnosis) and as a continuous variable (reflecting the number of IgG-positive food items). The selection of covariates for the regression models was based on the clinical significance or if their inclusion altered the effect estimate by more than 10% (refer to Supplemental Table 1). Four analytical models were developed for a comprehensive understanding: Model 1: unadjusted; Model 2: adjusted for age, sex, and BMI; Model 3: further adjustment included smoking history and fatty liver disease; Model 4: additionally controlled for γ-GT, Cr, UA, TG, HDL-C, FPG, hemoglobin, and CEA.

The association between FSsIgGR and CAs was further examined using a dose–response relationship through a restricted cubic spline model, which facilitated the construction of smooth curves to illustrate this relationship. Subgroup analysis, based on the previously mentioned covariates, was conducted to explore the association across different demographic and clinical subgroups, enhancing the understanding of how specific variables may influence the relationship. In addition, a mediation effect analysis was undertaken to assess the role of BMI in the incidence of CAs attributable to FSsIgGR. This analysis helps to delineate whether BMI acts as a mediator in this relationship, potentially offering insights into targeted intervention strategies.

The largest missing value in our data was 754 (smoking history), accounting for 8.57% of the total sample size. To address the issue of missing data, multiple imputation using the chained equation approach was applied, utilizing the "mice" package in R software.[22] This method, involving five imputations, aimed to increase statistical power and reduce bias introduced by missing data. Furthermore, sensitivity analysis was conducted using both the original dataset, which included missing data, and a trimmed dataset that excluded all missing covariates. This approach allowed for the evaluation of the robustness of the study findings and assessed how different analytic models might influence the associations observed. The effect sizes and

p-values derived from all these models were documented and compared.

All statistical analyses were performed using R statistical software (version 4.2.2, available at http://www.R-project.org; The R Foundation). Statistical significance was defined as a *p*-value less than 0.05, using a two-sided test.

Results

Characteristics of participants

The study included a total of 8796 eligible participants, divided into 2703 individuals diagnosed with CAs and 6093 without polyps. The mean age was 50.1 years, with a male predominance of 70.1%. Baseline characteristics, stratified by the presence of CAs, are detailed in Table 1. Participants with CAs exhibited a higher mean age and BMI, and a greater prevalence of conditions such as fatty liver disease and diabetes mellitus compared to the polyp-free group (all $p < 0.001$). In addition, the proportion of participants who either smoked or consumed alcohol was lower in the CAs group. Furthermore, the quantity and positive grades of FSsIgGR were lower, and some routine laboratory tests—such as those for liver and kidney function, inflammatory markers, and blood glucose levels—were generally higher than in the non-polyp group (all $p < 0.05$). There were no significant differences between groups in terms of family history of colorectal cancer, or histories of cholecystectomy or appendectomy (all $p > 0.05$).

The study investigated the prevalence of IgG responses to 21 food antigens. Notably, eggs (32.12%), beer yeast (12.52%), wheat (9.07%), garlic (7.44%), and milk (7.07%) exhibited the highest rates of IgG positivity, with eggs showing a significantly higher rate compared to other foods. A marked gender difference was observed, where the rate of IgG positivity was significantly higher among females (67.9%) compared to males (56.6%), a difference that was statistically significant ($\chi^2 = 98.69$, $p < 0.001$). This gender disparity was consistent across most food antigens, suggesting a potential biological influence of gender on the occurrence of FSsIgGR. In addition, stratified analysis by age and BMI indicated that IgG positivity rates generally decreased with increasing age and BMI. However, specific foods such as beer yeast and mushrooms exhibited higher positivity rates among the elderly, potentially reflecting physiological and metabolic changes associated with aging (refer to Supplemental Figure 1).

Association between FSsIgGR and CAs

The selection of covariates for statistical analysis was based on their clinical relevance or if their inclusion led to a change in the effect estimate of more than 10%, as shown in Supplemental Table 1. These covariates were analyzed using univariate analysis to explore their relationship with CAs, detailed in Supplemental Table 2. Statistically significant covariates from the univariate analysis were then included in the multivariable analysis. The results of the multivariable logistic regression analysis, after multiple imputation of missing data, are presented in Table 2. This analysis examined the relationship between FSsIgGR and the risk of CAs. It demonstrated that both the number of IgG-positive foods and the levels of IgG were negatively associated with the risk of developing CAs, with adjusted odds ratios (ORs) of 0.94 (95% confidence interval (CI): 0.91–0.97; $p < 0.001$) and 0.97 (95% CI: 0.96–0.99; $p < 0.001$), respectively. After adjusting for potential confounders in Models 2–4 of Table 2, these associations remained statistically significant, albeit slightly attenuated (adjusted OR = 0.97; 95% CI: 0.93–0.99; $p = 0.037$ for the number of IgG-positive foods and adjusted OR = 0.99; 95% CI: 0.97–0.99; $p = 0.043$ for levels of IgG). These findings suggest a protective effect of higher FSsIgGR against the occurrence of CAs, potentially indicating an immunological or inflammatory role for specific dietary antigens in reducing the risk of CAs.

After categorizing the continuous variables of FSsIgGR into groups, the unadjusted model indicated a slightly reduced risk of CAs for individuals with FSsIgGR compared to those without (OR = 0.9; 95% CI: 0.82–0.98; $p = 0.02$). However, this association was no longer statistically significant when additional confounding factors were accounted for (see Models 2–4: $p > 0.05$). Furthermore, no significant relationships were found between SFGR or MFGR and the risk of CAs, suggesting that other factors may mediate the relationship between FSsIgGR and CAs. Sensitivity analysis conducted using the original dataset with missing data and a dataset from which all missing covariates were removed

Table 1. Characteristics of the included participants.

Variables	Total ($n = 8796$)	No colorectal polyps ($n = 6093$)	Colorectal adenomas ($n = 2703$)	p
Demographics				
Age (years), mean ± SD	50.1 ± 8.0	49.1 ± 8.1	52.4 ± 7.3	<0.001
Sex, *n* (%)				<0.001
Male	6162 (70.1)	3952 (64.9)	2210 (81.8)	
Female	2634 (29.9)	2141 (35.1)	493 (18.2)	
BMI (kg/m^2), mean ± SD	25.2 ± 3.3	24.9 ± 3.3	25.9 ± 3.2	<0.001
Medical history				
Family history of colorectal cancer, *n* (%)				0.272
No	8573 (97.5)	5946 (97.6)	2627 (97.2)	
Yes	223 (2.5)	147 (2.4)	76 (2.8)	
History of cholecystectomy, *n* (%)				0.679
No	8491 (96.5)	5885 (96.6)	2606 (96.4)	
Yes	305 (3.5)	208 (3.4)	97 (3.6)	
History of appendectomy, *n* (%)				0.823
No	8317 (94.6)	5759 (94.5)	2558 (94.6)	
Yes	479 (5.4)	334 (5.5)	145 (5.4)	
Fatty liver disease, *n* (%)				<0.001
No	3980 (45.2)	3006 (49.3)	974 (36)	
Yes	4816 (54.8)	3087 (50.7)	1729 (64)	
Diabetes mellitus, *n* (%)				<0.001
No	7885 (89.6)	5541 (90.9)	2344 (86.7)	
Yes	911 (10.4)	552 (9.1)	359 (13.3)	
Smoking history, *n* (%)				<0.001
No	4821 (59.9)	3617 (64.9)	1204 (48.8)	
Current	2574 (32.0)	1573 (28.2)	1001 (40.6)	
Abstain	647 (8.0)	384 (6.9)	263 (10.7)	
Drinking history, *n* (%)				<0.001
No	2825 (35.0)	2185 (39)	640 (25.9)	
Current	5079 (62.9)	3312 (59.1)	1767 (71.4)	
Abstain	176 (2.2)	108 (1.9)	68 (2.7)	

(Continued)

Table 1. (Continued)

Variables	Total ($n = 8796$)	No colorectal polyps ($n = 6093$)	Colorectal adenomas ($n = 2703$)	p
FSsIgGR conditions				
Quantity, M (Q1, Q3)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	<0.001
Level, M (Q1, Q3)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	2.0 (0.0, 3.0)	<0.001
Classification, *n* (%)				0.001
Negative	3520 (40.0)	2389 (39.2)	1131 (41.8)	
SFGR	2592 (29.5)	1772 (29.1)	820 (30.3)	
MFGR	2684 (30.5)	1932 (31.7)	752 (27.8)	
Laboratory data				
ALT (U/L), M (Q1, Q3)	19.1 (13.8, 27.5)	18.5 (13.5, 27.0)	20.4 (14.8, 28.6)	<0.001
AST (U/L), mean ± SD	19.6 ± 9.0	19.4 ± 8.8	20.1 ± 9.5	0.001
γ-GT (U/L), M (Q1, Q3)	28.0 (17.0, 48.0)	26.0 (16.0, 44.0)	33.0 (21.0, 55.0)	<0.001
Cr (μmol/L), mean ± SD	68.8 ± 14.0	67.8 ± 14.0	71.0 ± 13.7	<0.001
UA (μmol/L), mean ± SD	348.8 ± 89.5	342.1 ± 89.9	364.1 ± 86.6	<0.001
ALB (g/L), mean ± SD	44.7 ± 5.8	44.7 ± 3.2	44.8 ± 9.3	0.654
TC (mmol/L), mean ± SD	4.7 ± 0.9	4.7 ± 0.9	4.8 ± 0.9	0.162
TG (mmol/L), M (Q1, Q3)	1.5 (1.1, 2.2)	1.4 (1.0, 2.1)	1.6 (1.1, 2.4)	<0.001
HDL-C (mmol/L), mean ± SD	1.2 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	<0.001
LDL-C (mmol/L), mean ± SD	3.1 ± 0.8	3.1 ± 0.8	3.1 ± 0.9	0.258
FPG (mmol/L), mean ± SD	5.5 ± 1.1	5.5 ± 1.1	5.7 ± 1.2	<0.001
HbA1c (%), mean ± SD	5.8 ± 0.7	5.7 ± 0.7	5.9 ± 0.8	<0.001
Neutrophils, mean ± SD	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.049
Lymphocytes, mean ± SD	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	<0.001
Hemoglobin (g/L), mean ± SD	144.3 ± 15.4	142.9 ± 15.8	147.5 ± 13.8	<0.001
CRP (mg/dL), M (Q1, Q3)	0.1 (0.0, 0.2)	0.1 (0.0, 0.1)	0.1 (0.0, 0.2)	0.01
CEA (μg/L), M (Q1, Q3)	1.7 (1.1, 2.4)	1.6 (1.1, 2.3)	1.8 (1.2, 2.7)	<0.001
Carbohydrate antigen 199 (U/mL), M (Q1, Q3)	8.4 (5.7, 13.0)	8.4 (5.7, 12.9)	8.6 (5.7, 13.2)	0.426
Carbohydrate antigen 724 (U/mL), M (Q1, Q3)	2.0 (1.1, 4.5)	2.0 (1.1, 4.4)	2.0 (1.1, 4.6)	0.481
Carbohydrate antigen 125 (U/mL), M (Q1, Q3)	8.8 (6.7, 11.8)	8.9 (6.8, 12.0)	8.6 (6.4, 11.4)	<0.001

γ-GT, gamma-glutamyl transferase; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CEA, carcinoembryonic antigen; Cr, creatinine; CRP, C-reactive protein; FPG, fasting plasma glucose; FSsIgGR, food-specific serum immunoglobulin G reactivity; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MFGR, multiple FSsIgGR; SD, standard deviation; SFGR, single FSsIgGR; TC, total cholesterol; TG, triglycerides; UA, uric acid.

Table 2. Multivariable logistic regression analysis of FSsIgGR conditions and the risk of CAs with data after multiple imputation.

Variables	*n* Total	*n* Event (%)	Model 1		Model 2		Model 3		Model 4	
			OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Quantity of FSsIgGR	8796	2703 (30.7)	0.94 (0.91–0.97)	**<0.001**	0.96 (0.93–0.99)	**0.019**	0.96 (0.93–0.99)	**0.029**	0.97 (0.93–0.99)	**0.037**
Level of FSsIgGR	8796	2703 (30.7)	0.97 (0.96–0.99)	**<0.001**	0.98 (0.97–0.99)	**0.023**	0.99 (0.97–0.99)	**0.037**	0.99 (0.97–0.99)	**0.043**
FSsIgGR										
No	3520	1131 (32.1)	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
Yes	5276	1572 (29.8)	0.9 (0.82–0.98)	**0.02**	0.96 (0.87–1.06)	0.387	0.96 (0.87–1.06)	0.437	0.97 (0.88–1.07)	0.534
Classification of FSsIgGR										
Negative	3520	1131 (32.1)	1 (Ref.)		1 (Ref.)		1 (Ref.)		1 (Ref.)	
SFGR	2592	820 (31.6)	0.98 (0.88–1.09)	0.682	1.03 (0.92–1.15)	0.661	1.03 (0.92–1.15)	0.622	1.04 (0.93–1.16)	0.531
MFGR	2684	752 (28)	0.82 (0.74–0.92)	**<0.001**	0.89 (0.79–1)	0.05	0.9 (0.8–1.01)	0.07	0.91 (0.81–1.02)	0.094

Model 1: unadjusted. Model 2: adjusted for age, sex, and BMI. Model 3: adjusted for Model 2 parameters + smoking history and fatty liver disease. Model 4: adjusted for Model 3 parameters + γ-GT, Cr, UA, TG, HDL-C, FPG, hemoglobin, and CEA.
γ-GT, gamma-glutamyl transferase; BMI, body mass index; CAs, colorectal adenomas; CEA, carcinoembryonic antigen; CI, confidence interval; Cr, creatinine; FPG, fasting plasma glucose; FSsIgGR, food-specific serum immunoglobulin G reactivity; HDL-C, high-density lipoprotein cholesterol; MFGR, multiple FSsIgGR; OR, odds ratio; SFGR, single FSsIgGR; TG, triglycerides; UA, uric acid.
The bold values indicate $p<0.05$ (statistically significant).

yielded consistent results (refer to Supplemental Tables 3 and 4), underscoring the robustness of our findings. We further analyzed the relationship between FSsIgGR and different pathological types, including tubular adenomas, tubulovillous adenomas, villous adenomas, and adenomatous hyperplasia. The analysis indicated that in the FSsIgGR-positive population, the proportion of tubular adenomas and adenomatous hyperplasia was greater than in the FSsIgGR-negative population, whereas the more malignant tubulovillous adenomas and villous adenomas were more common in the FSsIgGR-negative population ($p=0.025$, refer to Supplemental Table 5).

To further investigate the relationship between the number of FSsIgGR and the risk of CAs, we applied a curve-fitting method, adjusting for multiple variables. The estimated dose–response curve, depicted in Figure S2, revealed a significant linear correlation between the number of FSsIgGR and the risk of CAs (p for non-linearity $=0.591$). This analysis was adjusted using the covariates from Model 4 in Table 2 and excluded the top 0.5% of data points measuring FSsIgGR to mitigate the impact of outliers. The results of the curve fitting indicated a significant decrease in the risk of CAs as the number of IgG-positive foods increased. This observation suggests that a higher count of FSsIgGR is associated with a reduced risk of developing CAs, aligning with our previous findings from the multivariable logistic regression analysis and further substantiating the inverse relationship between FSsIgGR and the risk of CAs.

Subgroup analysis and mediation analysis

To demonstrate the robustness of our findings, we conducted a subgroup analysis to determine whether the negative relationship between the quantity of FSsIgGR and the risk of CAs was consistent across various subgroups (refer to Figure 2). The results of this analysis showed that the negative correlation persisted across different age groups, genders, BMI categories, fasting

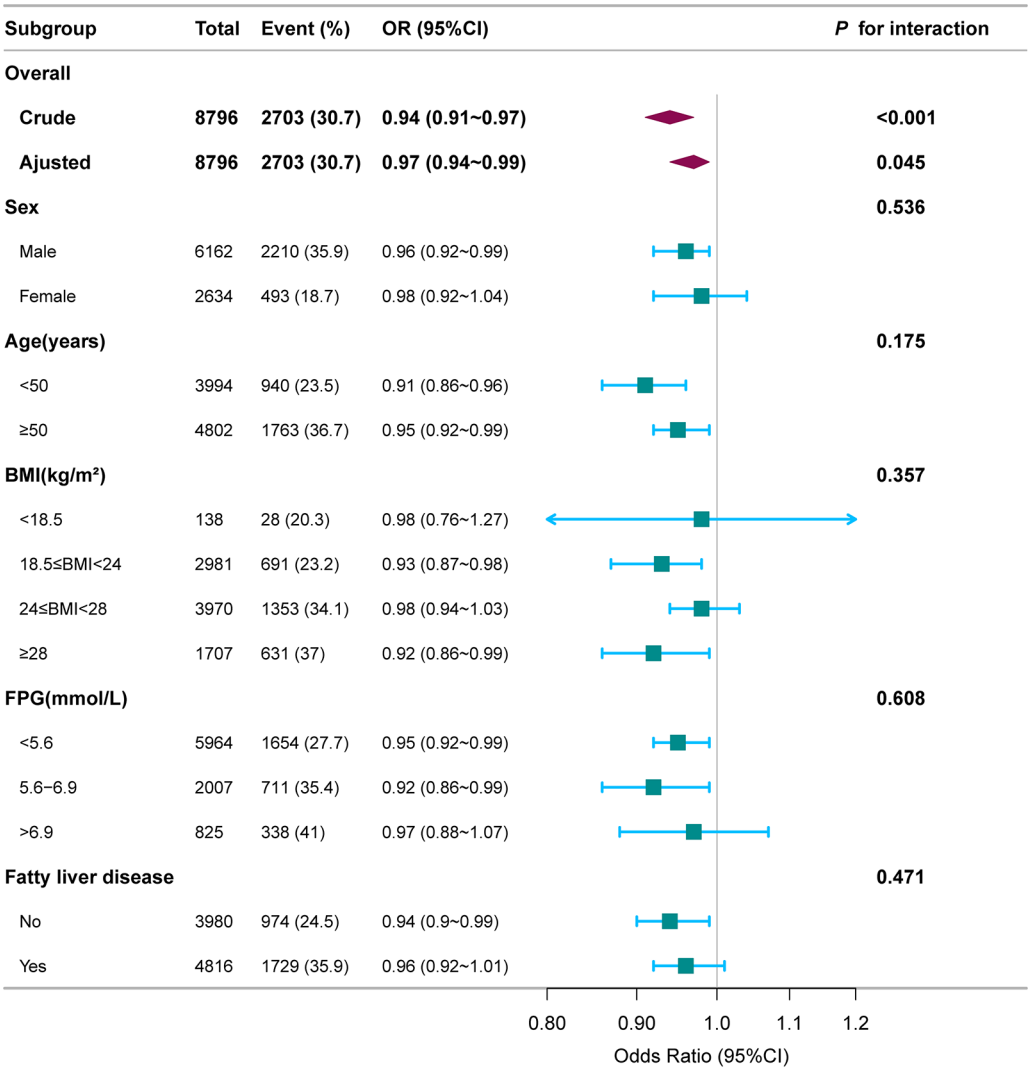

Figure 2. Subgroup analysis evaluating the relationship between the quantity of FSsIgGR and the risk of CAs.
BMI, body mass index; CAs, colorectal adenomas; FPG, fasting plasma glucose; FSsIgGR, food-specific serum immunoglobulin G reactivity.

blood glucose levels, and fatty liver conditions, with no significant interactions observed ($p > 0.05$). This consistency across diverse demographic and clinical subgroups further reinforces the reliability of our conclusions regarding the protective effect of FSsIgGR against CAs.

Figure 3 elucidates the mediating role of BMI in the relationship between the number of IgG-positive foods and the risk of CAs. After adjustments for age and gender, the analysis revealed that the total effect of the number of IgG-positive foods on CAs risk was −0.0083, and the effect mediated through BMI was −0.0005. This suggests that BMI significantly mediates the association between the number of IgG-positive foods and CAs, with a mediation ratio of 6.02% ($p = 0.038$). Notably, the subgroup analysis highlighted that the negative correlation between the number of FSsIgGR and CAs was statistically significant within specific BMI ranges: from 18.5 to 24 and ⩾28 kg/m². By contrast, within other BMI categories, this relationship did not achieve statistical significance, which warrants further exploration to understand these variations.

Discussion

This study uncovered a significant negative correlation between FSsIgGR and the incidence of

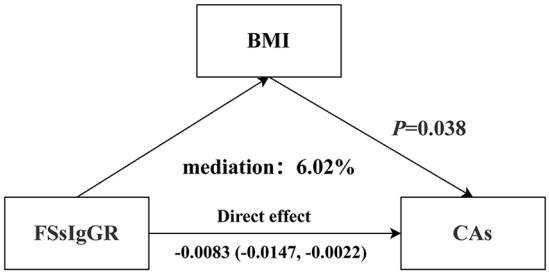

Figure 3. The mediating effect of BMI on the association between the quantity of FSsIgGR and the risk of CAs.
Adjusted for age, sex, smoking history, fatty liver disease, γ-GT, Cr, UA, TG, HDL-C, FPG, hemoglobin, and CEA.
γ-GT, gamma-glutamyl transferase; BMI, body mass index; CAs, colorectal adenomas; CEA, carcinoembryonic antigen; Cr, creatinine; FPG, fasting plasma glucose; FSsIgGR, food-specific serum immunoglobulin G reactivity; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid.

CAs within the Chinese population. This correlation remained consistent across various statistical models, although its significance slightly diminished when FSsIgGR was categorized. Subgroup analysis confirmed the persistent negative association across different ages, genders, and BMI categories. Sensitivity analysis reinforced the robustness of these findings, particularly evidence in the dose–response analysis, which showed a linear decrease in CAs risk with an increase in the number of IgG-positive food types. In addition, BMI was identified as a significant mediator in the relationship between FSsIgGR and CAs, contributing to 6.02% of the observed reduction in adenoma risk. It is worth noting that although our study demonstrates statistical significance, the effect sizes are small, particularly with CIs with upper bounds approaching 1.0. Therefore, the implications for clinical practice may be minimal.

Existing studies on dietary habits and the risk of CAs indicate that a diet high in saturated fats and low in fiber is associated with an increased risk of these lesions.[23] Conversely, our findings demonstrate a negative correlation between FSsIgGR and the risk of CAs, offering new insights into how dietary factors might modulate this risk. Supporting this perspective, Byrd et al.[5] found that diets rich in fiber, fruits, and vegetables, and low in fats correlate with a reduced risk of CAs. However, Kim et al.[24] contend that dietary changes alone may not adequately reduce the recurrence risk, highlighting the intricate interplay between diet, immune response, and adenoma development.

FSsIgGR is an immune response of the human body to food antigens. Under normal circumstances, the immune system recognizes and tolerates food antigens; however, in certain cases, it may perceive food antigens as potential threats and produce specific IgG antibodies.[25] This reaction is typically delayed, meaning that symptoms may appear hours or even days after the ingestion of specific foods. The delayed immune response involves multiple mechanisms, including normal immune tolerance and potential immune dysregulation. It is important to clarify that the production of FSsIgGR is a natural immune response to prolonged exposure to food antigens. The presence of IgG antibodies does not necessarily indicate a current state of food intolerance or allergy, as they may merely reflect a history of prior exposure.[26,27]

Research shows that gut IgG antibodies possess antigen specificity essential for maintaining the microenvironment's homeostasis, responding not only to pathogens but also to commensal microbes and self-antigens[28] In addition, the sialylation of IgG antibodies' Fc regions modifies their anti-inflammatory properties. This alteration diminishes their affinity for Fcγ receptors, thereby promoting an anti-inflammatory cascade critical for regulating intestinal inflammatory responses.[29] These insights suggest that preventive strategies for CAs should consider both the diet's nutritional composition and its impact on the immune system and inflammatory responses via IgG-related mechanisms.

In our study, BMI was identified as a significant mediating variable that influences the relationship between FSsIgGR and the risk of CAs, demonstrating a mediation effect ratio of 6.02%. This observation suggests that FSsIgGR may mitigate the risk of CAs through its impact on body weight and associated inflammatory pathways. The underlying biological mechanisms likely involve immune modulation and enhancement of gut barrier integrity. Further supporting evidence is found in the literature, indicating a connection between intestinal inflammation, obesity, and CAs: individuals consuming a diet high in inflammatory components are at an increased risk of colorectal cancer in obese populations.[30] In

addition, diet-induced weight loss has been shown to significantly diminish colorectal inflammation in obese premenopausal women, thereby potentially reducing CAs risk.[31]

Existing research has confirmed that high BMI facilitates the development of CAs, underscoring the importance of weight management and dietary regulation in reducing inflammation associated with elevated BMI as a preventative strategy against CAs.[32,33] In addition, alterations in the gut microbiota composition, particularly in individuals with FSsIgGR, may also decrease the risk of CAs by enhancing gut barrier functionality and modulating immune responses.[34] Specific probiotics, such as *Lactobacillus rhamnosus* GG, have been shown to mitigate inflammation related to high BMI and confer protection against CAs through their roles in modifying the gut environment and immune function.[35] These insights carry substantial practical implications for clinicians and dietitians. Evaluating FSsIgGR can inform personalized dietary plans that not only alleviate intolerance symptoms but also manage BMI as a preventive measure against CAs. This comprehensive approach integrates dietary adjustments, weight control, and gut health management, thereby enhancing the effectiveness of interventions aimed at reducing the risk of CAs and offering a more targeted preventive strategy.

Given the findings of this study, future research should prioritize investigating the specific biological mechanisms through which FSsIgGR influences the risk of CAs, potentially mediated by BMI or other factors. Experimental or longitudinal observational studies are particularly well-suited to provide deeper insights into these associations. Such studies could explore the local immune changes in the intestinal mucosa induced by FSsIgGR, thereby helping to validate the mechanisms proposed in this study. Furthermore, in light of the potential impact of FSsIgGR on CAs risk, it is advisable to conduct interventional studies that test specific dietary interventions tailored to the spectrum of IgG responses. These studies could not only confirm the association but also inform the development of novel preventive strategies that incorporate dietary management.

Limitation

This study employed a large sample size and reliable statistical methods to investigate the relationship between FSsIgGR and CAs, thereby enhancing the reliability and depth of the findings. In particular, conducted within the Chinese population, it represents the first study to address this research gap in this demographic, offering novel insights and directions for CAs risk studies across diverse global ethnicities. However, the study's cross-sectional design poses a limitation, as it restricts the ability to establish causal relationships and merely allows for correlation inferences between FSsIgGR and CAs. In addition, the interpretation of the results could be impacted by the omission of a comprehensive analysis of potential confounding factors, such as the detailed dietary habits and preferences of the participants or environmental factors that cannot be measured. Future research should adopt prospective or experimental designs and meticulously capture dietary habits and other pertinent lifestyle factors more extensively to more accurately elucidate the relationship. Moreover, replicating these findings in diverse populations will help determine if the observed effects are consistent across different ethnic and dietary backgrounds, thereby validating the universality of the results.

Conclusion

This study found that FSsIgGR is negatively associated with the risk of CAs in the Chinese population, and BMI plays a partial mediating role in this association. However, due to the retrospective design of this study, causality cannot be determined. Future longitudinal studies are needed to verify these associations and explore their potential mechanisms. This study suggests that FSsIgGR may provide new insights for the prevention of CAs, but further research is required to confirm this.

Declarations

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of the Chinese PLA General Hospital (Registration Number: S2023-238-02, Approval Date: October 19, 2023) and complied with the principles of the Helsinki Declaration. In addition, we confirm that all procedures were conducted in accordance with relevant guidelines and regulations. The data are anonymous, and the requirement for informed consent was therefore waived.

Consent for publication
Not Applicable.

Author contributions
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Acknowledgements
We express our heartfelt gratitude to all participants, staff members, and fellow researchers for their invaluable contributions.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The data presented in this study are available on request from the corresponding author due to privacy.

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Supplemental material
Supplemental material for this article is available online.

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