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ORIGINAL ARTICLE

Mortality trends of colorectal cancer among overweight patients at the global and national levels

Fei Cao[1] · Feng Li[2] · Lei Shi[1] · Lei Zhang[1] · Tianjiang Ma[1] · Guoyao Zhang[1]

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Abstract

Purpose Colorectal cancer (CRC) is a commonly diagnosed malignancy with highly heterogeneous incidence and mortality rates worldwide. High body mass index (BMI) is a well-defined risk factor for CRC. The mortality trends of CRC among patients who are overweight contributions at the global and national levels are largely unknown.

Method We collected data on CRC-related mortality attributable to high BMI from 1990 to 2017 from the Global Burden of Disease Study 2017 database. The annual average percentage change (AAPC) was used to quantify the CRC age-standardized mortality rate (ASMR) trends.

Results Globally, approximately 896,040 CRC-related deaths occurred in 2017, among which 73,222 (8.2%; 54,193 in men and 19,029 in women) deaths were attributable to high BMI. The high-BMI-related CRC ASMR increased from 0.81 per 100,000 in 1990 to 0.93 per 100,000 in 2017, with an AAPC of 0.42 (95% CI 0.36, 0.49). The increasing trend was consistent among populations of different sexes and ages. A more pronounced increase was found in men and in regions with middle or low socio-demographic indexes.

Conclusion The increase in high-BMI-related CRC mortality suggests scarce attention to overweight in the current prevention strategies and highlights its priority in future prevention strategies for CRC.

Keywords Colorectal cancer · Mortality · High BMI · Global burden of disease

Introduction

Colorectal cancer (CRC) is a commonly diagnosed malignancy worldwide. More than 1.8 million new CRC cases and 881,000 CRC-related deaths were estimated to have occurred in 2018; based on these data, CRC ranks third in terms of incidence and second in terms of mortality [1]. The incidence of CRC is highly heterogeneous across the world, and the highest incidence was observed mostly in developed countries (e.g., the USA and Australia), in which the incidence of CRC has been reported to be decreasing due to the effects of enormous efforts over the last decade [2]. Nevertheless, an increasing trend of CRC incidence was found in countries such as China, in which CRC was less-commonly diagnosed [3].

The risk factors for CRC have been extensively investigated [4]. For example, high intake of red and processed meats, physical inactivity, and alcohol consumption may increase the risk of CRC, regardless of sex and ethnicity [5–7]. Among these risk factors, obesity or overweight (defined as a high body mass index, BMI) is the most substantial risk factor for CRC [8, 9]. During the last four decades, the prevalence of high BMI (defined as BMI ≥ 25 kg/m^2) among adults increased from 21% in men and 24% in women to nearly 40% in both sexes globally [10]. The increasing prevalence of high BMI in almost all countries indicates poor health and a heavy disease burden [10, 11]. For instance, 7% of colorectal cancers in women (42,300 cases) and 6% in men (42,200 cases) worldwide in 2012 were attributable to excess body weight [11]. Each 5-unit increase in BMI is associated with a 5% increase in CRC risk [12]. As the prevalence of high BMI increases worldwide, the disease burden of CRC is expected to increase further in the next few decades. Knowing the global distribution and temporal trends of CRC mortality that is attributable to high BMI is critical for the global control of CRC.

Fei Cao and Feng Li contributed equally to this work.

✉ Guoyao Zhang
guoyaozhang_123@163.com

[1] Department of Oncology, Luohe Central Hospital, People's East Road 54, Luohe City 462000, Henan Province, China

[2] Department of General Surgery, People's Hospital of Shenqiu, Zhoukou City 466000, Henan Province, China

In this study, we comprehensively analysed the temporal trend of CRC mortality among overweight patients at the global and national levels based on the Global Burden of Disease Study from 2017. Our results can be used to assess the current prevention strategies for CRC and are helpful for the design of targeted strategies for CRC prevention tailored to different countries and populations.

Materials and methods

Study data

We collected data on CRC-related mortality attributable to high BMI by sex, country or territory, single calendar year, and age from 1990 to 2017 using the Global Burden of Diseases (GBD) database online query tool (Global Health Data Exchange) [13]. Data from a total of 195 countries or territories and 5 socio-demographic index (SDI) regions were collected. Data from males, females, both sexes, and three age categories (i.e., 15–49, 50–64, and ≥ 70 years) and age-standardized mortality rate (ASMR) were retrieved from the GBD online database. The data of CRC mortality attributable to high BMI were derived from the Risk Factors Study comparative risk assessment (CRA) framework, which is a comprehensive and comparable approach to risk factor quantification that offers a useful tool for synthesizing evidence on risks and risk-outcome associations [14]. The details of CRA have been presented in a previous study [14]. In brief, the relative risk by the level of exposure or by cause of mortality can be found in previous primary studies or in secondary studies that summarize relative risks. Specifically, for risk-outcome pairs in this study, namely, high BMI-CRC, a systematic review was conducted to identify relevant studies providing causality between this risk-outcome pair. In this study, overweight or high BMI was defined as BMI ≥ 25 kg/m^2. The national human development index (HDI), an integrated index measuring average achievement in three basic dimensions of human development, including a long and healthy life, knowledge, and a decent standard of living, was collected from the World Bank website (www.worldbank.org).

Statistical analysis

The annual average percentage change (AAPC) was applied to quantify the CRC mortality trends by sex, country, SDI, and age from 1990 to 2017. As described in previous studies [3, 15], AAPC is a summative and widely used measure of ASMR trend over a specific interval and can be calculated by a regression model, i.e., $y = \alpha + \beta x + \varepsilon$, where y = ln(ASMR) and x = calendar year. The AAPC was calculated as $100 \times (\exp(\beta) - 1)$. We conducted a Pearson correlation test to assess the correlations of the AAPCs of high-BMI-related CRC mortality with HDIs from 2015 at the national level. All statistical tests were analysed using the R program (R core team, version 3.3.3, Vienna, Austria). A P value < 0.05 was considered statistically significant.

Results

Globally, approximately 896,040 CRC-related deaths occurred in 2017, among which 73,222 (8.2%; 54,193 in men and 19,029 in women) deaths were attributable to high BMI. The high-BMI-related CRC ASMR increased from 0.81 per 100,000 in 1990 to 0.93 per 100,000 in 2017, with an AAPC of 0.42 (95% CI 0.36, 0.49). The CRC AMSR attributable to high BMI increased by 0.58% per year (95% CI 0.51, 0.65) in men during the study period, whereas it decreased by 0.23%

Table 1 The age-standardized mortality rate and its estimated annual percentage change in colorectal cancer attributable to high body mass index by sex from 1990 to 2017

	ASMR[a]		AAPC[b] (95% CI)
	1990	2017	
Global			
Both	0.81	0.93	0.42 (0.36, 0.49)
Male	1.28	1.53	0.58 (0.51, 0.65)
Female	0.46	0.44	− 0.23 (− 0.30, − 0.16)
High SDI			
Both	1.53	1.56	− 0.09 (− 0.21, 0.03)
Male	2.66	2.69	− 0.11 (− 0.24, 0.02)
Female	0.74	0.64	− 0.71 (− 0.81, − 0.61)
High-middle SDI			
Both	0.82	1.13	1.16 (1.03, 1.28)
Male	1.26	1.84	1.39 (1.26, 1.52)
Female	0.51	0.57	0.29 (0.16, 0.41)
Middle SDI			
Both	0.25	0.54	3.08 (3.00, 3.15)
Male	0.35	0.83	3.47 (3.36, 3.57)
Female	0.16	0.28	2.19 (2.16, 2.23)
Low-middle SDI			
Both	0.19	0.41	2.90 (2.84, 2.96)
Male	0.26	0.60	3.17 (3.13, 3.20)
Female	0.12	0.24	2.58 (2.47, 2.68)
Low SDI			
Both	0.13	0.25	2.51 (2.45, 2.58)
Male	0.18	0.36	2.72 (2.64, 2.79)
Female	0.07	0.14	2.37 (2.28, 2.45)

ASMR age-standardized mortality rate, *AAPC* estimated annual percentage change, *BMI* body mass index, *SDI* socio-demographic index, *CI* confidence interval

[a] ASMR (per 100,000) in 2017

[b] AAPC between 1990 and 2017

per year (95% CI 0.16, 0.30) in women (Table 1; Fig. 1). Regarding the SDI region, the high-BMI-related CRC ASMR increased in all SDI regions in both sexes, with the exception of the high SDI region, in which the ASMR was highest and remained stable from 1990 to 2017 (Table 1; Fig. 1). The most pronounced increase was observed in the middle SDI region (AAPC = 3.08, 95% CI, 3.00, 3.15). Men experienced more significant increases in high-BMI-related CRC mortality than women at the global and regional levels. The CRC ASMR attributable to high BMI increased in all three age groups (Table 2; Fig. 2). The greatest increase was observed in people aged 15–49 years (AAPC = 1.42, 95% CI 1.29, 1.55), followed by people aged ≥ 70 years (AAPC = 0.55, 95% CI 0.46, 0.64) and people aged 50–69 years (AAPC = 0.28, 95% CI 0.19, 0.38).

In 2017, the number of CRC-related deaths with high BMI as a risk factor was highest in the USA (11,290), followed by China, Russia, and Germany. High-BMI-related CRC mortality was highest in the Virgin Islands (ASMR = 3.48 per 100,000), followed by Hungary, Slovakia, and Serbia (Fig. 3). Between 1990 and 2017, a total of 167 countries or territories experienced a significant increase in high-BMI-related CRC ASMR (Fig. 3). The greatest increase was found in Equatorial Guinea (AAPC = 6.58, 95% 6.04, 7.13), followed by the Philippines, Nepal, and Pakistan. Only 20 countries or territories experienced a significant decrease in high-BMI-related CRC ASMR (Fig. 3), and among these countries, most were developed countries. The most pronounced decrease was detected in Iraq (AAPC = − 1.31, 95% CI − 1.48, − 1.13), followed by Kyrgyzstan, Austria, and Bahrain. The temporal trends were partially consistent in men and women at the national level. In men, the CRC ASMR attributable to high BMI increased, remained stable, and decreased in 170, 7, and 18 countries or territories, respectively. The greatest increase was observed in Equatorial Guinea (AAPC = 6.79, 95% CI 6.31, 7.29), followed by the Philippines, Nepal, and Saudi Arabia. The greatest decline was found in Austria (AAPC = − 1.50, 95% CI − 1.68, − 1.32), followed by Iraq, Kyrgyzstan, and Germany. In women, the CRC ASMR attributable to high BMI increased, remained stable, and decreased in 151, 14, and 30 countries or territories, respectively. The most pronounced increase was found in Equatorial Guinea (AAPC = 6.44, 95% CI 5.74, 7.14), followed by Nepal, the Philippines, and India. The most pronounced decrease was found in Austria

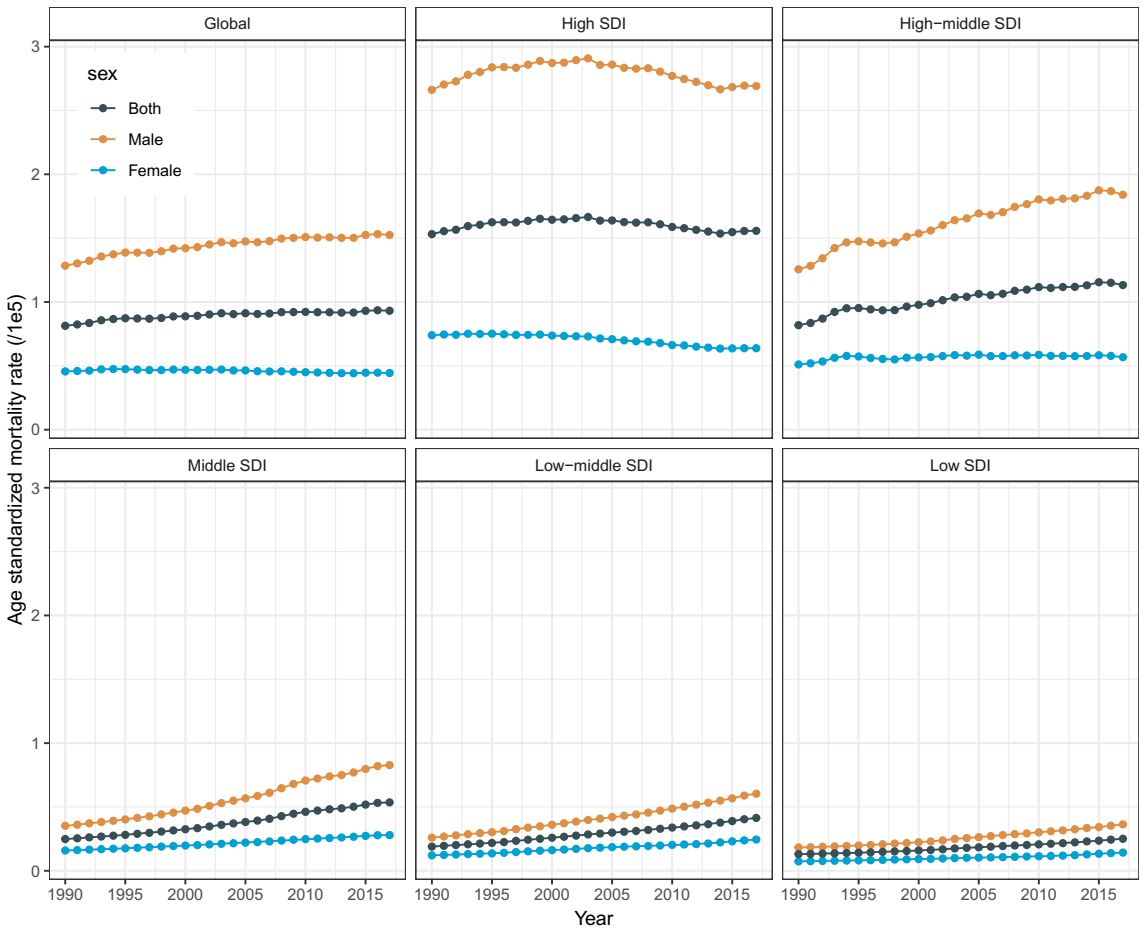

Fig. 1 The temporal trends of colorectal cancer mortality attributable to high body mass index from 1990 to 2017 by sex and socio-demographic index (SDI) region

Table 2 The age-standardized mortality rate and its estimated annual percentage change in colorectal cancer attributable to high body mass index by age from 1990 to 2017

	ASMR[a]		AAPC[b] (95% CI)
	1990	2017	
Global			
15–49	0.09	0.14	1.42 (1.29, 1.55)
50–69	2.03	2.33	0.28 (0.19, 0.38)
70+	7.30	8.58	0.55 (0.46, 0.64)
High SDI			
15–49	0.21	0.27	0.86 (0.64, 1.07)
50–69	4.36	4.34	− 0.30 (− 0.39, − 0.20)
70+	13.57	14.60	0.19 (0.08, 0.30)
High-middle SDI			
15–49	0.12	0.21	1.61 (1.36, 1.86)
50–69	2.40	3.03	0.43 (0.22, 0.63)
70+	6.39	9.85	1.73 (1.59, 1.87)
Middle SDI			
15–49	0.05	0.13	3.29 (3.07, 3.52)
50–69	0.62	1.41	3.26 (3.16, 3.35)
70+	1.87	4.25	3.32 (3.20, 3.44)
Low-middle SDI			
15–49	0.04	0.08	2.81 (2.73, 2.89)
50–69	0.51	1.11	2.85 (2.81, 2.89)
70+	1.38	3.18	3.05 (2.95, 3.15)
Low SDI			
15–49	0.02	0.05	2.85 (2.75, 2.95)
50–69	0.37	0.70	2.39 (2.30, 2.49)
70+	0.94	1.80	2.51 (2.45, 2.58)

ASMR age-standardized mortality rate, *AAPC* estimated annual percentage change, *BMI* body mass index, *SDI* socio-demographic index, *CI* confidence interval

[a] ASMR (per 100,000) in 2017

[b] AAPC between 1990 and 2017

(AAPC = − 1.91, 95% CI − 2.02, − 1.79), followed by Bermuda, Qatar, and Germany. Figure 4 displays a significant negative correlation of national HDIs with AAPCs of high-BMI-related CRC mortality. This result suggests that countries with a higher HDI mostly experienced a pronounced decrease in high-BMI-related CRC mortality.

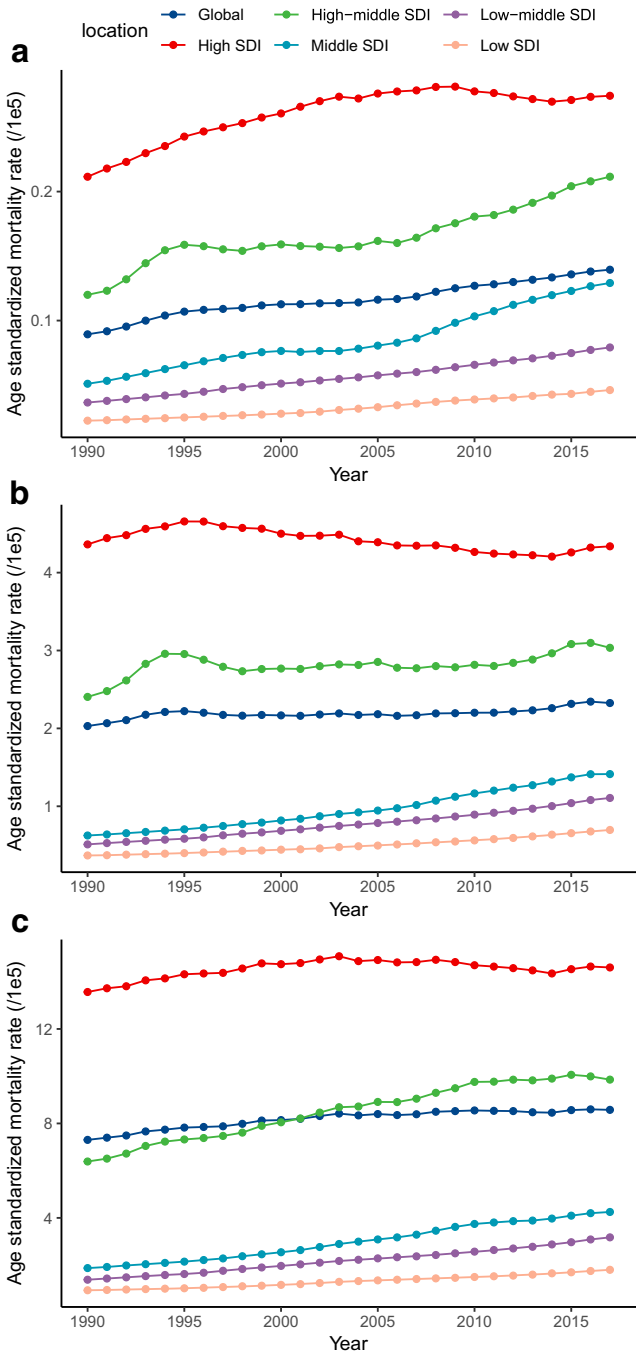

Fig. 2 The temporal trends of colorectal cancer mortality attributable to high body mass index from 1990 to 2017 by age and socio-demographic index (SDI) region (**a** 15–49 years; **b** 50–69 years; **c** 70+ years)

Discussion

In this study, we comprehensively described the disease burden of CRC attributable to high BMI and analysed the temporal trends of high-BMI-related CRC mortality at the global and national levels. In general, the CRC mortality attributable to high BMI was highly heterogeneous around the world, with the highest mortality found in North America and parts of Europe. The high-BMI-related CRC mortality rate increased annually during the last three decades regardless of sex, age, and region. A more pronounced increase was found in men and in regions with middle or low SDIs.

Overweight and obesity constitute the fifth leading cause of mortality, accounting for approximately 2.8 million adult deaths each year [9]. Large-scale epidemiological studies have demonstrated a consistent and compelling association between excess body weight and risk of cancer, independent of

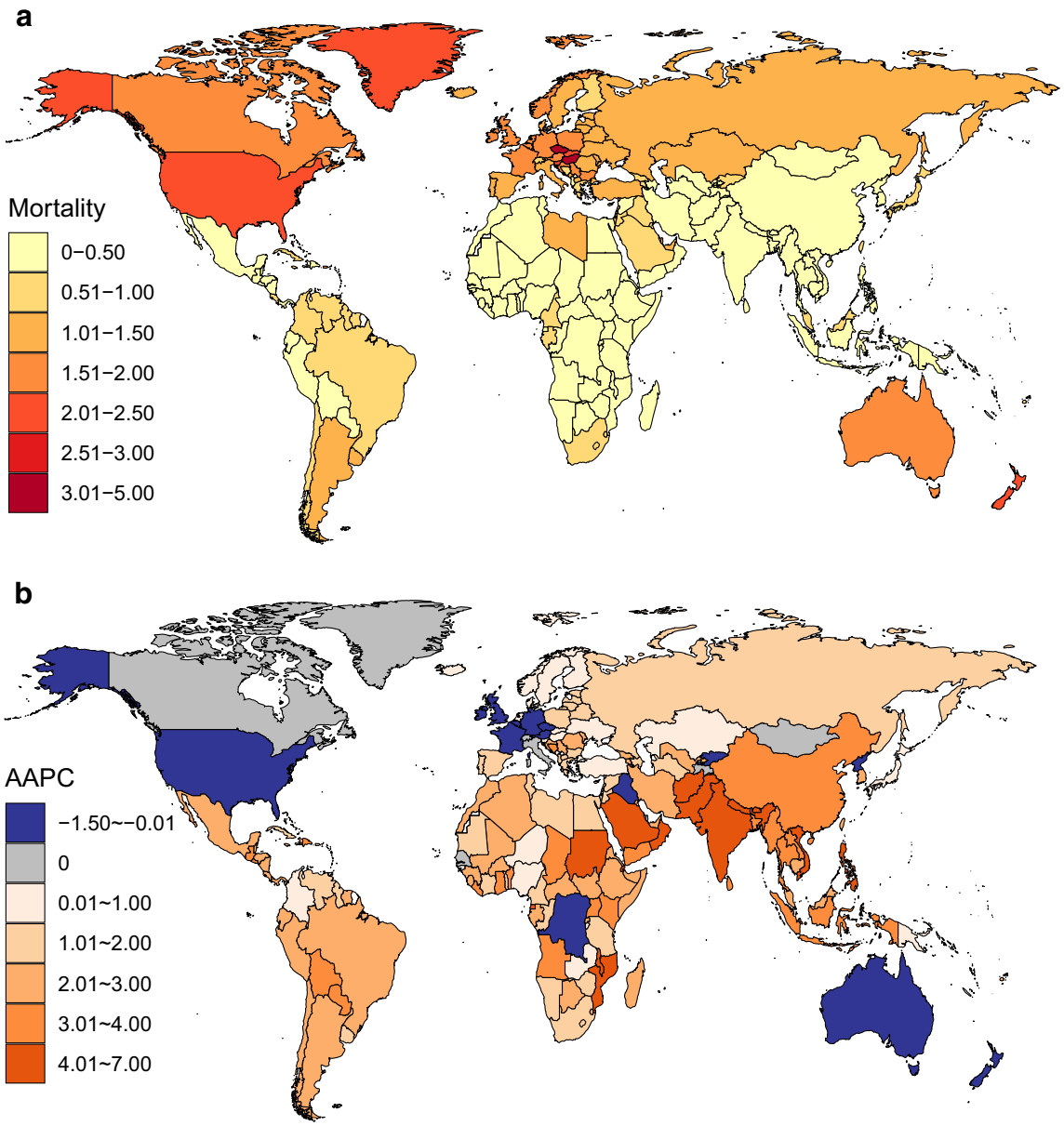

Fig. 3 Colorectal cancer mortality attributable to high body mass index at the national level in 2017 (**a**) and its estimated average percentage change (AAPC) between 1990 and 2017 (**b**). The non-significant AAPCs were forced to be zero and are mapped with grey

sex, age, and ethnicity [16–18]. Regarding CRC, previous studies have suggested that obesity is associated with a 30–70% increased risk of cancer in men, albeit the association is less significant in women [8, 19–21]. The underlying mechanisms that link obesity to CRC remain unclear, but a metabolic syndrome, insulin resistance, and modifications in levels of adipocytokines might be of great importance [9, 22, 23]. For instance, adipose tissue can produce various growth factors, hormones and cytokines, which are termed adipocytokines. The adipocytokines include leptin, resistin, visfatin, adiponectin (APN), and numerous cytokines (e.g., tumour necrosis factor α, interleukin (IL)-6, and IL-1 receptor agonist). It has been reported that obesity leads to an alteration in the levels of several adipocytokines, which may further contribute to an accelerated risk of CRC [24, 25]. Other biological factors mediating the association of overweight with CRC, such as the gut microbiota or bile acids, are emerging and require further investigation [26].

Given the increasing disease burden of CRC, a set of measures has been initiated to combat CRC over the last decades. Examples of these measures are as follows: (1) modifying the diet pattern, including increasing the intake of calcium, fibre, milk, and whole grains, and reducing the intake of red and processed meat; (2) improving weight management; and (3) expanding CRC early screening programmes among populations. These efforts have resulted in a decrease in CRC incidence in developed countries, such as the USA, in which the overall CRC incidence has decreased markedly by > 30%

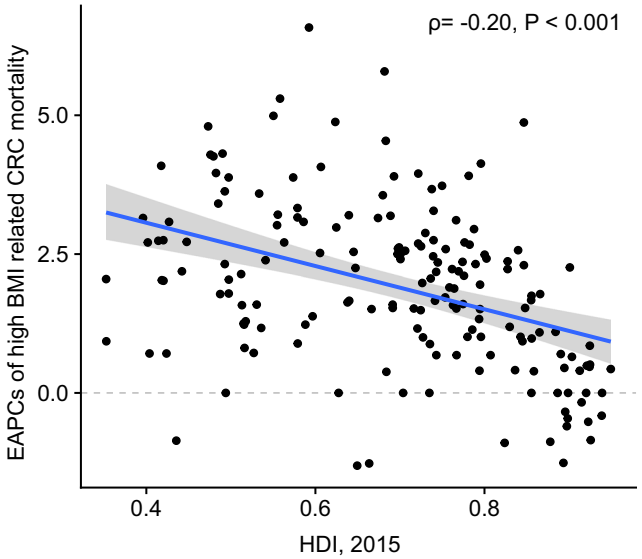

Fig. 4 The correlation of estimated annual percentage changes (AAPCs) in high-BMI-related colorectal cancer mortality with national human development index (2015). The ρ denotes the Pearson correlation coefficient. The *P* values were derived from the Pearson correlation test

from 1975 to 2013 [27]. However, an unfavourable trend was found in regions, such as countries in Asia, in which the CRC incidence was previously lower [3, 28]. The global increase in high BMI prevalence, on the one hand, might undermine the efficacy of current prevention strategies in developed countries and, on the other hand, might aggravate the disease burden of CRC in developing countries.

In the current study, we found that the CRC mortality attributable to high BMI increased at the global level and in more than 80% countries by different magnitudes. The increasing trend was more pronounced in developing countries than in developed countries, which was largely aligned with the temporal trend of high BMI prevalence [29]. We also observed an increase in high-BMI-related CRC mortality in a younger population, suggesting that high-BMI-related CRC morbidity and mortality will be further increased in the future if no effective interventions are introduced. Given the global increase in high-BMI-related CRC mortality, halting the increase in obesity among adults and children, and strengthening weight management deserve more priority in CRC prevention strategies. A consensus on evidence-based and cost-effective strategies to prevent and control obesity has recently been proposed, which emphasized the promotion of a healthy diet and physical activity through policy and system approaches [30, 31]. For example, (1) the governments and policymakers should play a pivotal role in reinforcing the importance of addressing the obesity problem and establishing more effective prevention strategies to combat it; (2) multifaceted solutions, involving government, industry, the civil society, and public sector, are warranted; (3) funds and investments should be allocated specifically to create an environment that promotes healthful eating and an active lifestyle, especially among children and adolescents; (4) interventions and campaigns aiming to improve the knowledge and skills for the prevention of obesity and body weight management, including setting-based health promotion and education programmes for school children, mass media campaigns, and social marketing for community residents, are needed; and (5) incorporating overweight and obesity into the CRC screening protocol [32].

The limitations of our study should be noted. First, the contribution of high BMI to CRC mortality was estimated by integrating pre-published data, which varied in data quality and therefore might introduce biases. Second, the estimated percentage change in CRC mortality should be interpreted with caution because in most cases, the lower the baseline mortality rate, the higher the magnitude of change.

In summary, CRC mortality attributable to high BMI increased in most countries during the last three decades. The alarming increase in high-BMI-related CRC mortality reveals the lack of attention to overweight in the current prevention strategies and highlights its priority in future strategies for CRC global control.

Contributors Study conception: GZ and LZ.
Data collection and analyses: FC, FL, and LZ.
Results interpretations: LZ, FL, FC, GZ, and LS.
Manuscript writing: LZ, FC, GZ, and LS.
Manuscript proofing: GZ, LZ, and TM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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