GeroScience (2025) 47:3343–3364
https://doi.org/10.1007/s11357-024-01375-x

ORIGINAL ARTICLE

Overweight and obesity significantly increase colorectal cancer risk: a meta-analysis of 66 studies revealing a 25–57% elevation in risk

Zoltan Ungvari · Mónika Fekete · Peter Varga · Andrea Lehoczki · János Tibor Fekete · Anna Ungvari · Balázs Győrffy

Received: 29 August 2024 / Accepted: 1 October 2024 / Published online: 8 October 2024
© The Author(s) 2024

Abstract The incidence of colorectal cancer (CRC) has been steadily rising, and obesity has been identified as a significant risk factor. Numerous studies suggest a strong correlation between excess body weight and increased risk of CRC, but comprehensive quantification through pooled analysis remains limited. This study aims to systematically review and meta-analyze the existing literature to evaluate the association between obesity and CRC risk, considering variations across sex and study designs. A systematic literature search was conducted in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science to identify randomized controlled trials and human clinical trials from 1992 to 2024. Statistical analysis was performed using the https://metaanalysisonline.com web application using a random effects model to estimate the pooled hazard rates (HR). Forest plots, funnel plots, and Z-score plots were utilized to visualize results. We identified 52 clinical trials and 14 case–control studies,

Z. Ungvari
Vascular Cognitive Impairment, Neurodegeneration and Healthy Brain Aging Program, Department of Neurosurgery, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Z. Ungvari
Stephenson Cancer Center, University of Oklahoma, Oklahoma City, OK, USA

Z. Ungvari
Oklahoma Center for Geroscience and Healthy Brain Aging, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Z. Ungvari
Department of Health Promotion Sciences, College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Z. Ungvari
International Training Program in Geroscience, Doctoral College/Institute of Preventive Medicine and Public Health, Semmelweis University, Budapest, Hungary

M. Fekete · P. Varga · A. Lehoczki · A. Ungvari (✉)
Institute of Preventive Medicine and Public Health, Semmelweis University, Semmelweis University, Budapest, Hungary
e-mail: Ungann2004@gmail.com

J. T. Fekete · B. Győrffy
Dept. of Bioinformatics, Semmelweis University, 1094 Budapest, Hungary

J. T. Fekete · B. Győrffy
Cancer Biomarker Research Group, Institute of Molecular Life Sciences, HUN-REN Research Centre for Natural Sciences, 1117 Budapest, Hungary

B. Győrffy
Dept. of Biophysics, Medical School, University of Pecs, 7624 Pecs, Hungary

encompassing a total of 83,251,050 and 236,877 subjects, respectively. The pooled analysis indicated that obesity significantly increased the prevalence of CRC (HR = 1.36, 95% CI = 1.24–1.48, $p < 0.01$). This effect was consistent across sexes, with HRs of 1.57 (95% CI = 1.38–1.78, $p = 0.01$) for males and 1.25 (95% CI = 1.14–1.38, $p < 0.01$) for females. Case–control studies specifically showed an effect, but with marginal significance only (HR = 1.27, 95% CI = 0.98–1.65, $p = 0.07$). The Z-score plot indicated the need for additional analysis in the case–control group. A significant heterogeneity was observed across studies in all four settings. This meta-analysis provides robust evidence that obesity is a significant risk factor for colorectal cancer, with an overall hazard rate indicating a 36% increased risk. The effect is pronounced across both sexes, with males showing a slightly higher risk compared to females. Although case–control studies showed a weaker association, the overall trend supports the link between obesity and CRC. These results underscore the importance of public health interventions aimed at reducing obesity to potentially lower the risk of colorectal cancer.

Keywords Epidemiology · Aging · Age-related disease · Malignancy · Neoplasm · Adiposity · Adipose · Colon carcinoma

Introduction

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality globally, with particularly high incidence rates in the European Union (EU) [1–5]. CRC is predominantly an age-related disease, with most cases occurring in individuals over the age of 50 [2, 4, 6]. This trend underscores the significant role of fundamental cellular and molecular aging processes in the development of CRC [6, 7].

Numerous studies have identified a variety of risk factors for CRC [8, 9], among which overweight and obesity are particularly prominent [10–75]. The growing prevalence of overweight and obesity has raised significant public health concerns [76], necessitating a deeper understanding of their impact on CRC risk. The obesity epidemic is a global phenomenon, with particularly high prevalence rates observed in developed regions such as the United States and the European Union (EU) [77, 78]. In the United States, the prevalence of obesity among adults has more than doubled since the 1970s, with current estimates indicating that over 40% of adults are obese [79–84]. Similarly, the EU faces a substantial obesity burden, with significant variations in obesity rates among member states [8, 78]. In 2019, the proportion of overweight adults in the EU varied significantly: for women, it ranged from 37% in Italy to 58% in Croatia, and for men, it ranged from 53% in France to 73% in Croatia [78]. Notably, Hungary stands out as one of the most obese nations in the EU, with nearly two-thirds of its adult population classified as overweight or obese in 2019 (67.3% for males and 53.3% for females) [78]. The prevalence of overweight and obesity among older adults is even more alarming: over 68% of adults aged 45 to 64, 76.4% of adults aged 65 to 74, and 67.3% of adults aged 75 and older were overweight or obese in 2019 [78]. Comparable trends are evident in other EU countries and the United States [84, 85], where high levels of overweight and obesity among both adults and the elderly signify a broader public health concern.

As the population ages, the intersection of obesity and aging [79] becomes increasingly critical in understanding CRC risk. Older adults are particularly vulnerable to obesity-related health issues [86–96], including CRC, as the cumulative effects of prolonged obesity can exacerbate age-related cellular damage, senescence, and inflammation [97–103]. Accordingly, there is emerging data suggesting that obesity in aging populations may pose a more significant risk for CRC compared to younger individuals. Epidemiological data show that the incidence rates of CRC rise sharply with age. When stratified by BMI, these rates are significantly higher in obese elderly populations compared to their normal-weight counterparts [5]. This alarming trend underscores the urgency of addressing obesity as a major public health issue. The implications are particularly profound for countries like the United States and Hungary, where the high prevalence of obesity could have significant repercussions for CRC incidence and outcomes. Understanding the link between overweight, obesity, and CRC risk is crucial for developing effective prevention and intervention strategies.

This meta-analysis aims to provide a comprehensive evaluation of the association between overweight

and obesity and the risk of colorectal cancer. By analyzing data from 66 studies, we seek to quantify the increased CRC risk associated with different levels of excess body weight. Our findings are expected to provide critical insights that will inform public health policies and interventions, particularly in regions with high obesity rates, to help mitigate the growing burden of colorectal cancer.

Methods

Search strategy

We conducted a systematic search of the PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science databases from 1992 to 2024 to identify studies examining the associations between overweight and obesity and the risk of colorectal cancer [10–61] (Fig. 1). The search terms used included "colorectal cancer," "body mass index," overweight, and obesity. Table 1 contains the combination of search terms used for the systematic review of overweight, obesity, and colorectal cancer risk. We excluded studies on cancer precursors such as colorectal adenomas because our primary objective was to evaluate the risk of CRC than precursor lesions. While adenomas are a known risk factor for CRC, including them could introduce variability due to the different natural histories and progression rates of adenomas to CRC.

Study eligibility assessment

The eligibility of each study was independently assessed by two researchers (AU, MF) [10–75]. We excluded studies that were not published as full reports, such as conference abstracts and letters to editors, studies focusing on cancer mortality (rather than incidence), and studies of cancer precursors (e.g., colorectal adenoma and/or polyps). The inclusion criteria for the studies incorporated into the meta-analysis are outlined in Table 2.

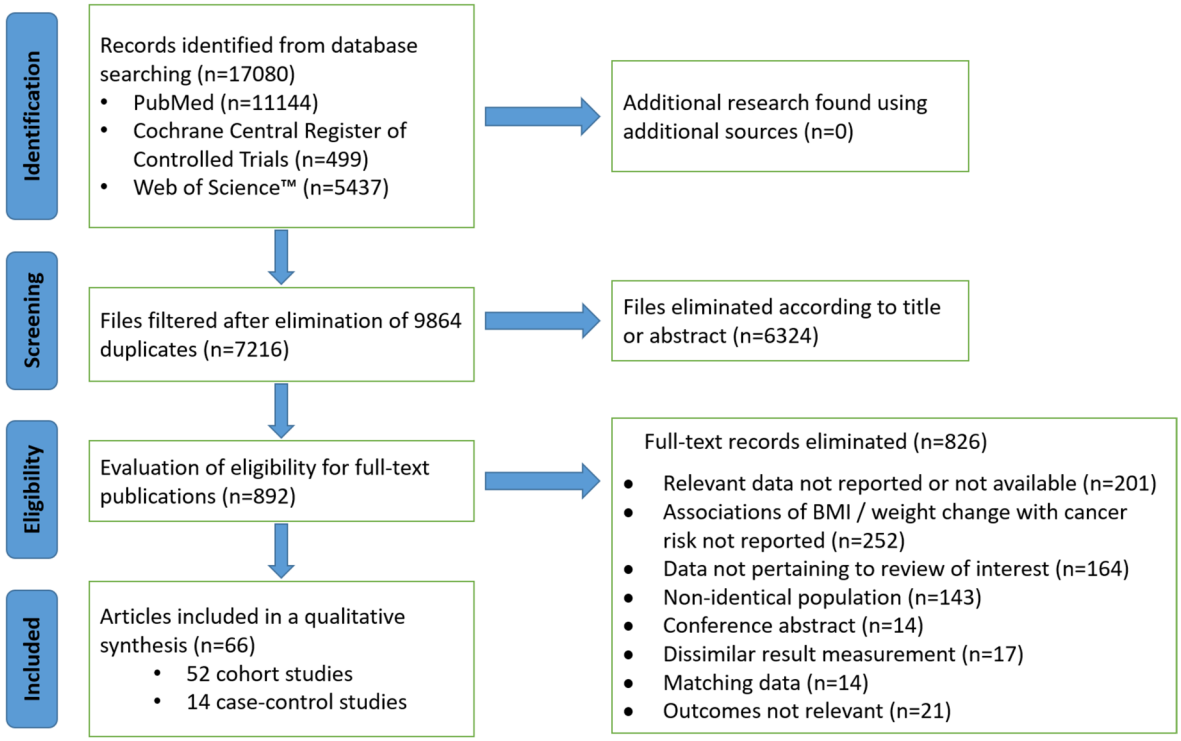

Fig. 1 Flow diagram of article selection process

Table 1 Search terms for systematic review on overweight, obesity, and colorectal cancer risk

Search focus	Search terms
Colorectal cancer and body mass index (BMI) in cohort studies	"colorectal cancer AND body mass index AND cohort study"
Colorectal cancer and obesity in case–control studies	"colorectal cancer AND obesity AND case–control study"
BMI and colorectal cancer risk in meta-analyses	"BMI AND colorectal cancer risk AND meta-analysis"
Obesity and colorectal cancer incidence in systematic reviews	"obesity AND colorectal cancer incidence AND systematic review"
Overweight and colorectal cancer risk estimates	"overweight AND colorectal cancer risk estimates"
BMI, obesity, and CRC risk	"BMI AND obesity AND colorectal cancer risk"
Body mass index and CRC incidence	"body mass index AND colorectal cancer incidence"
Colorectal cancer and adiposity	"colorectal cancer AND adiposity"
Risk estimates for CRC related to obesity	"risk estimates AND colorectal cancer AND obesity"
Hazard ratios for BMI and CRC	"hazard ratios AND body mass index AND colorectal cancer"
Relative risk of CRC with obesity	"relative risk AND colorectal cancer AND obesity"

Table 2 Inclusion criteria for studies included in the meta-analysis

Criteria	Description
Cohort studies	Included cohort studies that determined BMI at baseline and recorded cancer cases during follow-up
Risk estimates	Required each cohort study to report risk estimates (relative risks, odds ratios, or hazard ratios) with 95% confidence intervals, separately for men, women, or both
Case–control studies	Included nested case–control studies within cohort studies
Height and weight data	Included studies where height and weight (for BMI calculation) were self-reported or directly measured

Determining the overall effect

Statistical analysis was conducted using the web application available at https://metaanalysisonline.com. The random effects model was utilized to estimate pooled hazard rates (HR), odds ratios (OR), and their 95% confidence intervals (CI). Forest plots were generated to visualize both individual studies and summary results, providing a graphical representation of data variability and the overall effect estimate. Heterogeneity among the included studies was evaluated using the chi-squared test and I^2 index.

Funnel plots were created to assess the relationship between the estimated effects from each study and their precision, and to examine publication bias. Egger's test was performed to determine the significance of this bias.

Determining sample size robustness

Trial sequential analysis (TSA) was conducted to evaluate the robustness of the sample size. The a priori information size (APIS) was determined under a 10% risk ratio reduction with a two-sided α of 5% and a power (1 – β) of 80%. TSA analyses were performed in Stata 14.1 using the metacoumbounds package. A Z-score plot was created to visualize the relationship between the cumulative sample size, time, and cumulative Z-scores. This analysis helped assess whether the cumulative sample size was sufficient for conclusive inference or if additional studies were necessary.

Subcohort analysis settings

To provide a comprehensive understanding, we conducted the statistical analysis across several specific settings. First, we performed a combined analysis of all included studies to generate an overall effect estimate. Next, we carried out two separate analyses for men and women to explore potential gender-specific differences in the outcomes. Finally, we analyzed case–control studies independently, where individuals with colorectal cancer (cases) were compared to those without (controls). This multifaceted approach allowed us to assess the robustness and applicability

of our findings across different subgroups and study designs.

Results

Cohort studies for colorectal cancer (both sexes)

A total of 32 studies were analyzed incorporating results from both sexes [11, 18, 22, 27, 28, 32, 33, 35, 37–54, 56–61]. Using the random effects model with the inverse variance method to compare the hazard rates (HR), a statistically significant difference was found, with a summarized hazard rate of 1.36 and a 95% confidence interval of 1.24–1.48. The test for overall effect indicated significance at $p < 0.05$.

Significant heterogeneity was detected, suggesting inconsistent effects in magnitude and/or direction among the studies. The I^2 value of 97.2% indicates that most of the variability among studies is due to heterogeneity rather than random chance (see Fig. 2).

The funnel plot does not suggest potential publication bias. Egger's test does not support the presence of funnel plot asymmetry (intercept: 1.04, 95% CI − 1.76–3.84, t: 0.727, *p*-value: 0.473, depicted in Fig. 3A).

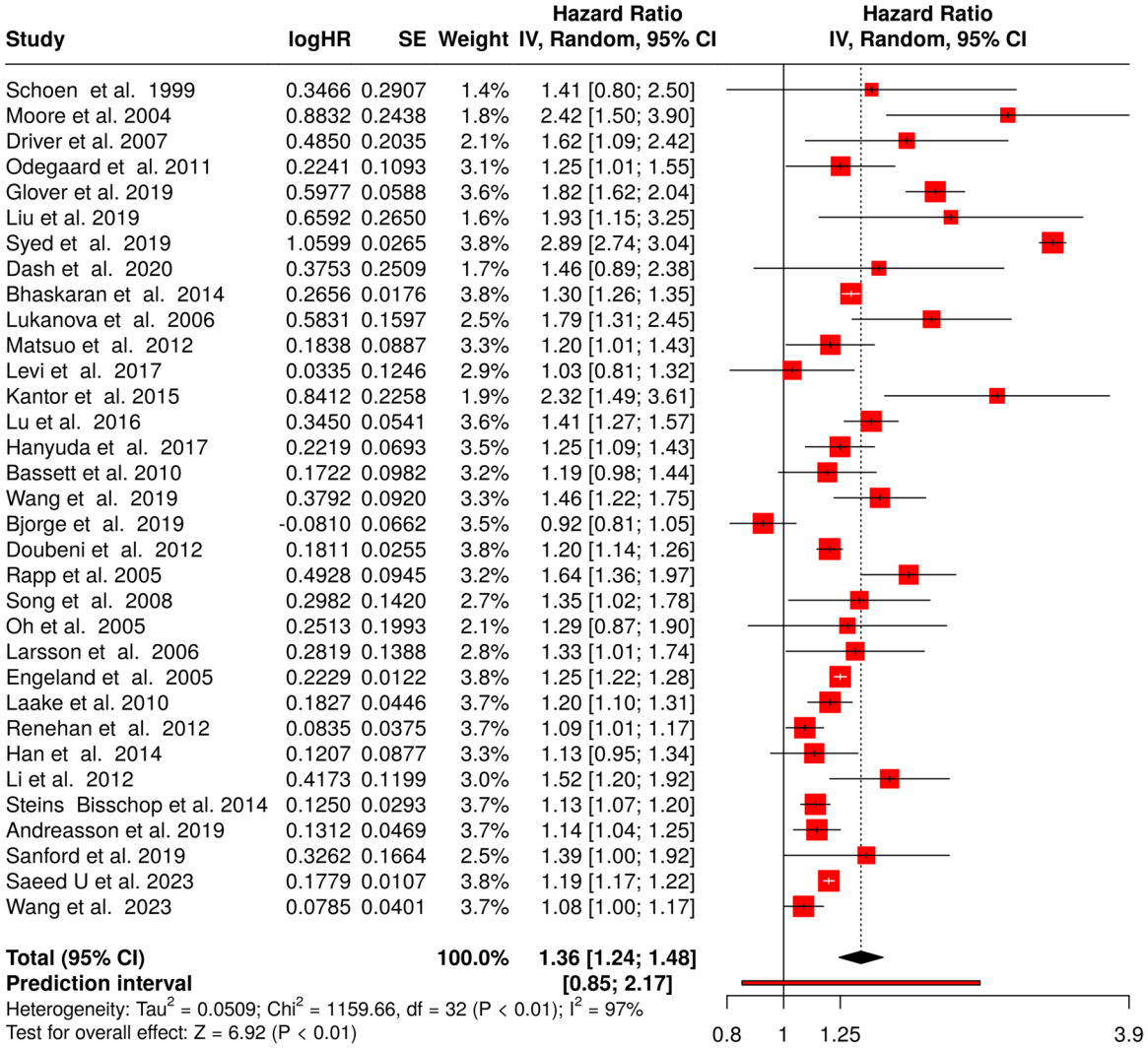

Fig. 2 Meta-analysis of cohort studies linking obesity and colorectal cancer in both sexes published between 1999 and 2023 shows a highly significant effect. HR, hazard rate; SE, standard error; CI, confidence interval; IV, inverse variance

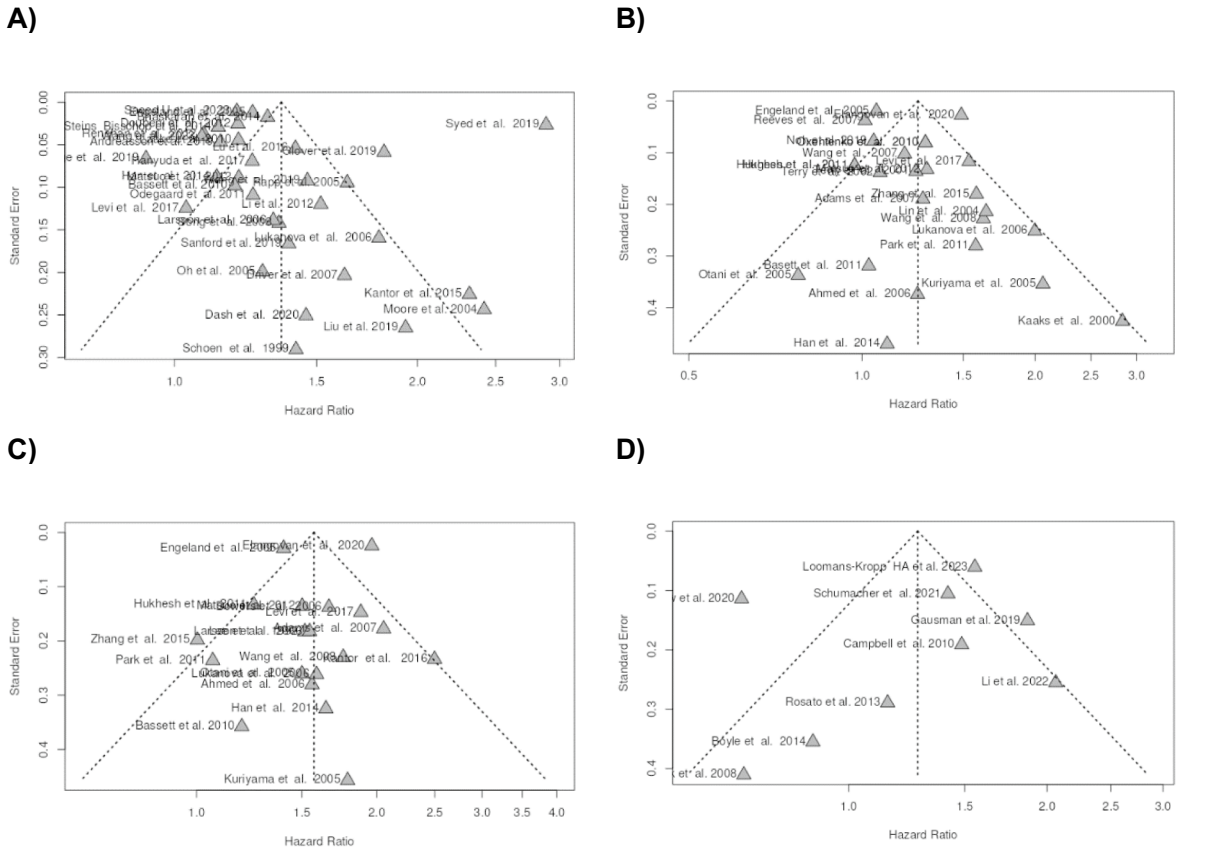

Fig. 3 Funnel plots indicate no potential publication bias in the four different setting analyzed, including cohort studies for CRC in both sexes (**A**), cohort studies for CRC in women (**B**), cohort studies for CRC in man (**C**), and case–control studies for CRC in both sexes (**D**)

Cohort studies for colorectal cancer—women

A total of 23 trials were included in the analysis [10–32]. Using the random effects model with the inverse variance method to compare hazard rates, a significant change was found, with a summarized hazard rate of 1.25 and a 95% confidence interval of 1.14–1.38. The test for overall effect showed significance at $p < 0.05$.

We observed a noteworthy heterogeneity, suggesting varying effects in scale and/or direction between the trials. The I^2 value of 84.6% specifies that most of the variability among studies is due to heterogeneity rather than accidental chance (presented in Fig. 4).

Based on the funnel plot, there is no publication bias. Egger's test does not support the presence of funnel plot asymmetry (intercept: 0.78, 95% CI − 0.54–2.1, t: 1.159, p-value: 0.258; shown in Fig. 3B).

Cohort studies for colorectal cancer—men

A total of 20 studies were used in this breakdown [10–12, 14, 17–22, 27–29, 31–36, 55]. Using the random effects model with the inverse variance method to liken hazard rates, a statistically significant difference was uncovered, with a summarized hazard rate of 1.57 and a 95% confidence interval of 1.38–1.78. The test for overall effect indicated significance at $p < 0.05$.

Notably, a substantial heterogeneity was present, suggesting varying effects in magnitude and/or direction amongst the studies. The I^2 value of 82.4% indicates that most of the variability among the results is

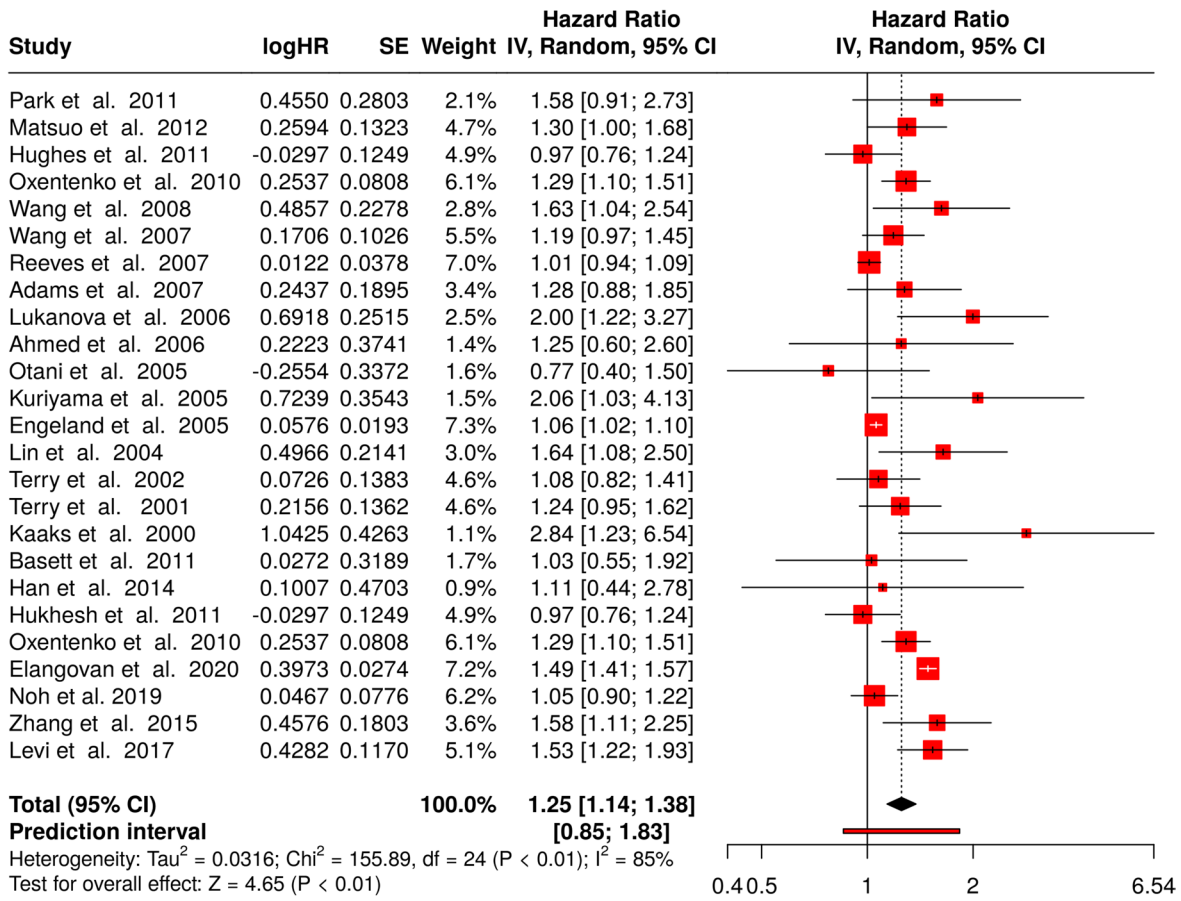

Fig. 4 Meta-analysis of cohort studies linking obesity and colorectal cancer in women published between 2001 and 2023 shows a significant effect. HR, hazard rate; SE, standard error; CI, confidence interval; IV, inverse variance

due to heterogeneity rather than casual chance (see Fig. 5).

The funnel plot does not suggest a likely publication bias. Egger's test does not back a significant funnel plot asymmetry (intercept: − 0.6, 95% CI − 1.99–0.79, t: − 0.843, *p*-value: 0.411; displayed in Fig. 3C).

Case–control studies for colorectal cancer—both sexes

A total of nine studies were evaluated [66, 67, 69–75]. Using the random effects model with the inverse variance method to compare hazard rates, no statistically significant difference was observed. The summarized hazard rate (HR) was 1.27 with a 95% confidence interval of 0.98–1.65, and the test for overall effect did not show significance (displayed in Fig. 6).

We have detected a significant heterogeneity, hinting at inconsistent effects in magnitude and/or direction among the studies. The I^2 value of 84.8% points to the observation that the majority of the observed variability is due to heterogeneity rather than random chance.

The funnel plot does not advocate any potential publication bias. Egger's test does not provide backing for the presence of a funnel plot asymmetry (intercept: − 1.04, 95% CI − 4.25–2.18, t: − 0.633, *p*-value: 0.547; see Fig. 3D).

Notably, the total number of cases ($n = 236{,}877$) included in the case–control analysis is below the a priori information size necessary for reaching statistical significance ($n = 283{,}345$), suggesting that the number of patients currently included in the case–control analysis is insufficient to draw

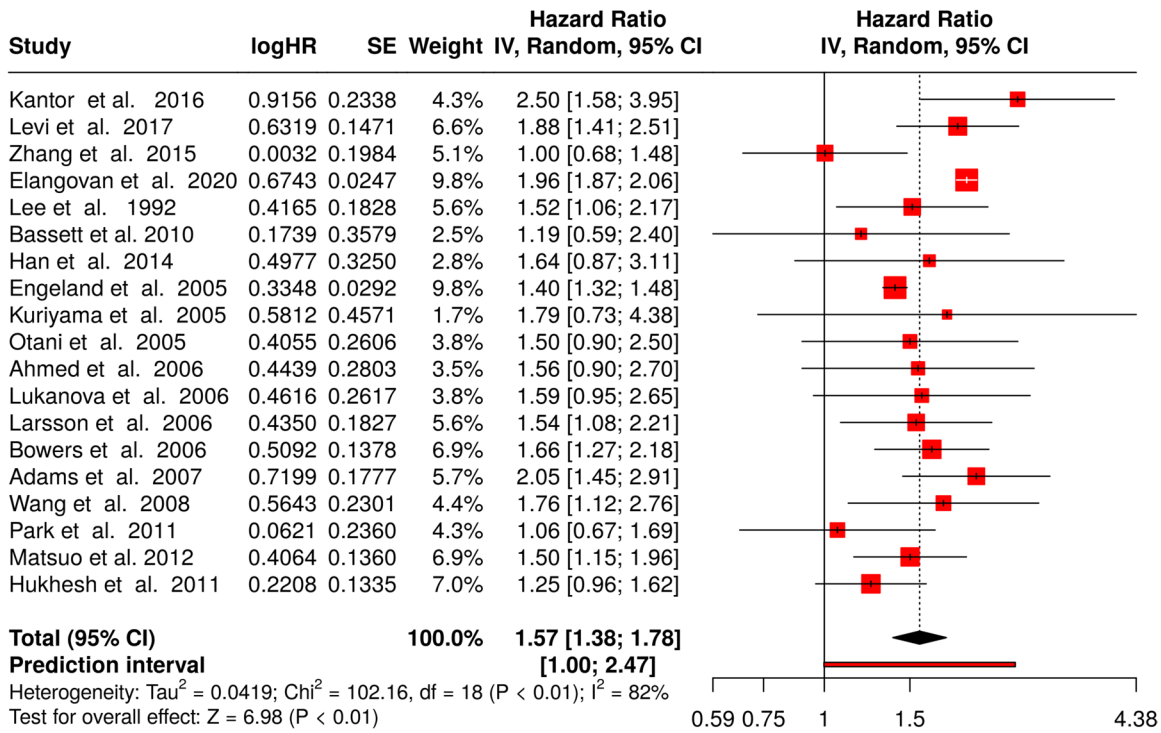

Fig. 5 Meta-analysis of cohort studies linking obesity and colorectal cancer in man published between 1992 and 2023 shows a highly significant effect. HR, hazard rate; SE, standard error; CI, confidence interval; IV, inverse variance

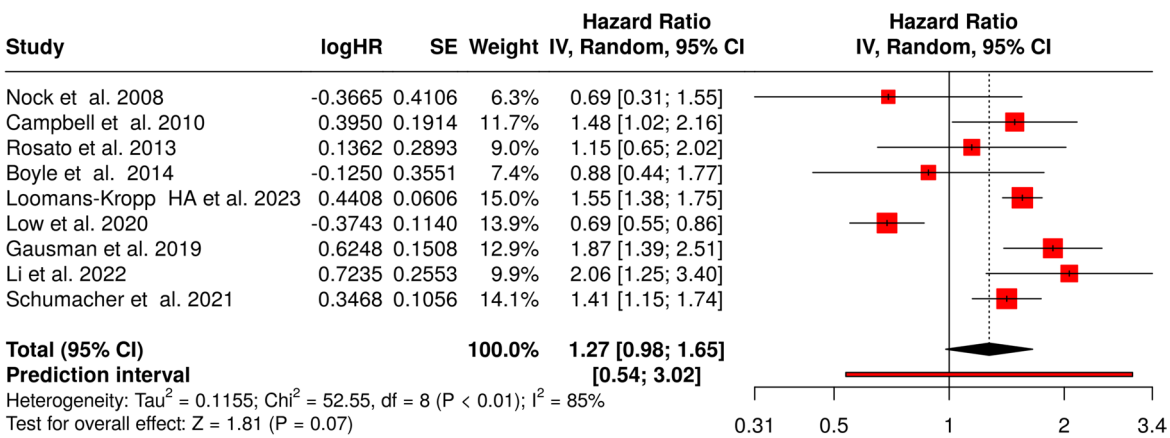

Fig. 6 Meta-analysis of case–control studies linking obesity and colorectal cancer in both sexes shows only a marginally significant effect. HR, hazard rate; SE, standard error; CI, confidence interval; IV, inverse variance

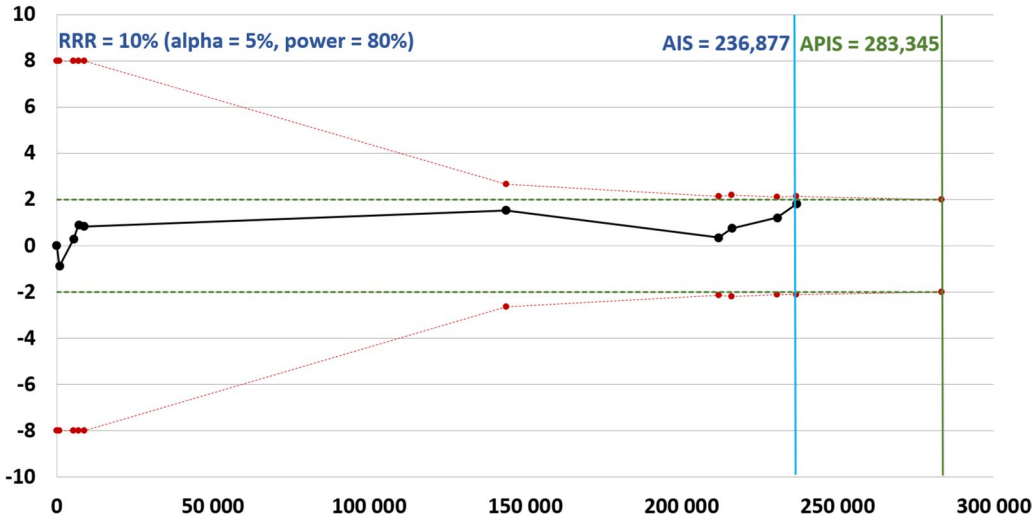

Fig. 7 Z-score plot of case–control studies investigating the correlation between obesity and colorectal cancer indicates the need of additional studies to reach a definitive conclusion. AIS, actual information size; APIC, a priori information size; RRR, relative risk reduction

a decisive conclusion and that further research is needed to validate present findings (Fig. 7).

Discussion

This meta-analysis provides compelling evidence that overweight and obesity are significant risk factors for CRC. Our results indicate that individuals with overweight or obesity have an elevated risk of CRC, with pooled hazard rates ranging from 1.25 to 1.57, depending on sex.

The findings from 52 cohort studies encompassing 83,251,050 participants show a consistent association between elevated BMI and increased CRC risk. For both men and women, being overweight or obese significantly raises the hazard rate for developing CRC, with men demonstrating a slightly higher risk (HR = 1.57) compared to women (HR = 1.25). These sex-specific differences may be attributable to biological factors, lifestyle differences, and varying fat distribution patterns between men and women. The case–control studies did not show a statistically significant association, which might be due to the smaller sample size compared to the cohort studies.

The increased morbidity and mortality of CRC in overweight and obese individuals can be attributed to several interrelated cellular and molecular mechanisms [104–106]. Overweight and obesity, which are associated with accelerated aging processes and increased biological age [89, 107], appear to similarly elevate the incidence of CRC across various molecular subtypes, as defined by specific molecular markers [108]. One significant factor is chronic inflammation, which is often elevated in individuals with excess body fat [104, 105, 109–112]. Adipose tissue, particularly visceral fat, secretes pro-inflammatory cytokines such as TNF-α, IL-6, and CRP, creating a systemic inflammatory environment [98, 113–121]. An important contributing factor appears to be the increased presence of senescent cells [122]. This chronic inflammation can lead to DNA damage and promote a tumorigenic environment in the colon. Furthermore, it also contributes to the pathogenesis of various other age-related diseases driven by inflammation, such as atherosclerosis [98, 113, 115, 118, 123–131]. Heightened inflammatory status likely also promotes tumor progression and metastasis [106]. Inflammatory mediators, growth factors, and other adipokines secreted from the visceral fat of obese patients likely impact cell proliferation, promote angiogenesis, activate mechanisms involved in invasion and metastasis, contribute to reprogramming energy metabolism, and modulate immune responses [106]. In obese patients, increased adipose tissue leads to higher levels of adipose stromal/stem cells

(ASCs) throughout the body, which can influence cancer progression by enhancing tumorigenesis and metastasis through multiple mechanisms, including the recruitment of ASCs to tumors and the production of cytokines and growth factors [132, 133]. Emerging evidence suggests that obesity alters the biological properties of ASCs, further promoting cancer development and spread [132]. Preclinical studies confirm that high fat diet-induced obesity per se significantly increases progression of a mouse colon cancer cell line in an orthotopic transplantation mouse model [134]. Additionally, obesity is associated with insulin resistance and hyperinsulinemia [135]. Elevated levels of insulin and insulin-like growth factor-1 (IGF-1) can promote cellular proliferation and inhibit apoptosis, further contributing to cancer development and progression [106, 136, 137]. Leptin, a hormone produced by adipose tissue, is another key player; in obese individuals, elevated leptin levels can enhance cell proliferation and angiogenesis while inhibiting apoptosis [138–144]. Conversely, adiponectin, which has anti-inflammatory and anti-proliferative effects, is typically reduced in obesity, removing a protective factor against cancer development [145, 146].

Moreover, obesity-induced alterations in the gut microbiota can influence CRC risk [147–149]. Dysbiosis, characterized by an imbalance in the gut microbial community, can lead to the production of carcinogenic compounds and promote an inflammatory state in the colon [147–150].

Furthermore, obesity can induce epigenetic changes that contribute to cancer initiation and/or progression [151–154]. Epigenetic modifications such as DNA methylation, histone modification, and non-coding RNA expression can alter gene expression patterns critical for cell growth, differentiation, and survival [152, 153]. These changes can lead to the activation of oncogenes and the silencing of tumor suppressor genes, facilitating cancer initiation and progression.

Lastly, oxidative stress, prevalent in obese individuals due to increased free fatty acids, adipokines, and dysregulation of proteins involved in production and elimination of ROS, can cause direct DNA damage and promote mutagenesis [155–158].

In addition to obesity-related increases in ROS production, aging itself is associated with a decline in cellular resilience to oxidative stress. A key factor in this decline is the dysfunction of nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that regulates the expression of antioxidant proteins protecting cells against oxidative damage triggered by metabolic stress [159–168]. In younger individuals, Nrf2 effectively maintains cellular redox homeostasis by activating the expression of detoxifying and antioxidant enzymes [86, 88, 160, 169–172]. However, with age, Nrf2 activity diminishes, leading to reduced expression of these protective enzymes and heightened vulnerability to oxidative stress. The dysfunction of Nrf2 in aging cells exacerbates the oxidative damage and inflammation associated with obesity. In an aged organism, the combined impact of obesity-induced oxidative stress and the natural age-related decline in Nrf2 function results in a significantly elevated oxidative burden. This heightened oxidative stress can further accelerate the development and progression of cancer [166]. We posit that in aged obese individuals, the reduced capacity to counteract ROS due to impaired Nrf2 function likely contributes to increased DNA damage, sustained inflammatory responses, and enhanced tumorigenic processes. The cumulative effect of these mechanisms not only increases the risk of CRC development but also contributes to more aggressive tumor phenotypes, leading to higher morbidity and mortality in overweight and obese individuals. Understanding these pathways is crucial for developing targeted therapies and prevention strategies to mitigate CRC risk in this population [166]. In particular, the interplay between obesity-related cellular oxidative stress and age-related decline in oxidative stress resilience underscores the need for targeted interventions that can enhance Nrf2 activity. Strategies aimed at boosting Nrf2 function or mimicking its activity [173] could potentially mitigate the oxidative damage and inflammation driving CRC in obese and aging populations. Thus, understanding the dual impact of obesity and aging on cellular oxidative stress mechanisms is critical for developing effective preventive and therapeutic approaches to reduce CRC risk in these vulnerable groups.

Obesity is not only a significant risk factor for CRC but is also associated with multiple other types of cancer, including cancers of the esophagus, gall bladder, pancreas, breast, endometrium, ovary, thyroid, kidney, and prostate as well as multiple myeloma [8, 174]. This broad association raises the possibility that similar mechanisms, including chronic inflammation and hormonal imbalances, contribute to

cancer development across these various organs [8]. Epidemiological studies estimate that 4–38% of cancers at these sites can be attributed to overweight and obesity, depending on the specific cancer type and sex [8]. Further highlighting the impact of obesity on cancer, data from Australia in 2013 indicated that 4.3% of all cancers diagnosed were attributable to overweight and obesity [174]. Analyzing age-specific incidence trends over the past 35 years for obesity-related cancers revealed that the incidence rate ratios (IRRs) for these cancers increased significantly, from 0.77 (95% CI 0.73, 0.81) for those born in 1903 to 2.95 (95% CI 2.58, 3.38) for the 1988 birth cohort, relative to the 1943 cohort [174]. In contrast, IRRs for non-obesity-related cancers remained stable, with non-significant decreases in younger cohorts [174].

Given the significant role of overweight and obesity in CRC [175–182], it is crucial to develop and implement strategies that effectively reduce BMI and to understand their impact on CRC risk. Further research into the effects of such interventions on CRC incidence will provide valuable insights into potential preventive measures, helping to shape more effective public health policies and individual treatment plans.

The potential of pharmacological treatments for obesity and their impact on CRC risk is an emerging area of study that holds promise for both cancer prevention and management. Incretin-based pharmacological interventions aimed at weight loss, such as GLP-1 receptor agonists (e.g., liraglutide and semaglutide), have demonstrated significant efficacy in reducing body weight and improving metabolic profiles in obese individuals [183, 184]. These medications work by enhancing insulin sensitivity, reducing appetite, and promoting satiety, leading to substantial weight loss. The reduction in body weight and improvement in metabolic health associated with these treatments could potentially lower CRC risk by mitigating obesity-related risk factors such as chronic inflammation, insulin resistance, and dyslipidemia. Studies have shown that GLP-1 receptor agonists not only aid in weight loss but also exhibit direct anti-cancer effects. For instance, research has indicated that these drugs can reduce the proliferation of colon cancer cells and induce apoptosis, thereby inhibiting tumor growth [185]. The potential dual benefit of weight reduction and direct anti-cancer activity could make GLP-1 receptor agonists a promising pharmacological option for reducing CRC risk in obese individuals. However, the real-life effect of these medications on CRC risk is not yet fully understood. Clinical trials assessing the efficacy and safety of these weight loss medications, including their direct effects on CRC incidence, are needed to establish their true impact. Much more research is required to determine the long-term outcomes and mechanisms by which these pharmacological treatments might influence CRC risk. This will involve comprehensive studies that include large, diverse populations and long follow-up periods to provide robust evidence on their role in cancer prevention.

Bariatric surgery is another intervention that has demonstrated significant reductions in obesity and associated comorbidities, which may impact incidence of CRC [186, 187]. Post-surgical weight loss leads to improvements in inflammatory markers, insulin sensitivity, and adipokine profiles, potentially contributing to a lower risk of CRC [186–188].

Public health interventions targeting obesity and overweight present a promising area for future research, particularly in understanding how these interventions can causally link to reduced CRC risk [149]. These interventions can range from comprehensive lifestyle programs to specific policy changes and workplace health promotions. Future studies could evaluate the effects of dietary interventions resulting in sustained reduction on BMI, on CRC risk[149]. Research should also investigate the impact of regular physical activity on CRC risk and determine the mediating effect of weight loss. Long-term cohort studies can provide data on how sustained physical exercise, tailored to different age groups and fitness levels, contributes to CRC prevention. Integrating behavioral counseling with dietary and physical activity interventions can be studied to assess its effectiveness in promoting sustained weight loss and reducing CRC risk [149]. The use of digital health tools and mobile applications to support these interventions could also be explored.

Consumption of various obesogenic foods, including sugar-sweetened beverages, has been linked to an increased risk of CRC [189–195]. Policies such as sugar-sweetened beverage taxes [196–199], subsidies for healthy foods, and regulations limiting unhealthy food marketing could be evaluated for their impact on obesity rates and subsequent CRC risk. Comparative studies across different regions implementing varying

levels of these policies could provide insights into their effectiveness.

Studies could examine the role of urban planning and the availability of recreational spaces in promoting physical activity and reducing obesity [200]. Longitudinal studies assessing changes in CRC incidence in communities before and after the introduction of such urban planning initiatives would be particularly informative.

Implementing and studying comprehensive workplace health programs that encourage physical activity, healthy eating [149], and regular health screenings can offer insights into reducing obesity [201] and CRC risk. Research could compare CRC incidence in organizations with robust health promotion programs to those without. Investigating the impact of policies that promote work-life balance, such as flexible working hours, on employees' physical activity levels and dietary habits could be beneficial. This could include assessing the CRC risk reduction in employees who participate in such programs. Investigating the impact of community-based public awareness campaigns on obesity and CRC risk could provide valuable insights. Studies could measure changes in community obesity rates and CRC incidence following targeted educational initiatives. Research could also focus on the long-term effects of school-based nutrition and physical activity programs on childhood obesity and subsequent adult CRC risk. Tracking cohorts of children exposed to these programs into adulthood would help establish the long-term benefits of early intervention. By exploring these diverse intervention strategies through well-designed studies, researchers can identify the most effective approaches to reduce obesity and, consequently, CRC risk. Establishing causal links between public health interventions and reduced CRC incidence will support the development of evidence-based policies and programs aimed at mitigating this significant health risk.

A major strength of this meta-analysis is the comprehensive inclusion of 66 studies, providing a robust assessment of the relationship between overweight, obesity, and CRC risk. The use of both cohort and case–control studies allows for a thorough examination of this association across different study designs and populations. However, the study is not without limitations. Significant heterogeneity among included studies suggests variability in study populations, methods, and potential confounders that could affect the results. Despite rigorous attempts to minimize bias, the potential for residual confounding cannot be entirely excluded. Potential factors contributing to this variability include differences in study populations (e.g., geographic region, age, ethnicity), variations in study design, and differences in how overweight and obesity were defined or measured. Additionally, lifestyle factors such as diet [202], physical activity [203], and access to healthcare likely varied across studies, which could influence CRC risk independently of obesity. Additionally, while funnel plots and Egger's test did not indicate significant publication bias, the possibility of unreported negative studies cannot be completely ruled out. Given the observed heterogeneity, more research is needed to understand the mechanisms driving sex differences in CRC risk associated with obesity [204]. Potential biological factors contributing to the higher CRC risk in obese men compared to women may include differences in fat distribution, with men more likely to accumulate visceral fat, which is associated with higher inflammation and metabolic dysfunction. Hormonal differences, such as the protective effects of estrogen in women, could also play a role. Additionally, lifestyle factors such as higher rates of smoking and alcohol consumption in men could interact with obesity to increase CRC risk. Additionally, long-term longitudinal studies assessing the impact of weight loss interventions on CRC incidence would offer valuable insights into potential preventive measures [149, 205]. Future research should explore the role of regular health screenings and weight management counseling in primary care settings. Studies could evaluate the effectiveness of integrating weight management into routine CRC screening and prevention programs, assessing how early intervention impacts long-term CRC risk [149].

In conclusion, this meta-analysis highlights the significant association between overweight, obesity, and increased CRC risk. With the obesity epidemic rising in regions like the United States and the European Union, there is an urgent need for effective public health interventions to address this modifiable risk factor. By mitigating obesity, it may be possible to substantially reduce the burden of CRC and improve population health outcomes. Public health policymakers and healthcare providers should prioritize obesity prevention and treatment as a key strategy in cancer prevention efforts. Enhanced public awareness,

lifestyle modifications, and targeted interventions could play a critical role in reducing the incidence of CRC and other diseases [107, 206, 207] linked to overweight and obesity, ultimately leading to better health outcomes and reduced healthcare costs.

Funding Open access funding provided by Semmelweis University. This work was supported by grants from the National Institute on Aging (RF1AG072295, R01AG055395, R01AG068295; R01AG070915), the National Institute of Neurological Disorders and Stroke (R01NS100782), and the National Cancer Institute (R01CA255840). AU was supported by TKP2021-NKTA-47, implemented with the support provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-NKTA funding scheme; by funding through the National Cardiovascular Laboratory Program (RRF-2.3.1–21-2022–00003) and by the National Laboratory for Drug Research and Development (PharmaLab, RRF-2.3.1–21-2022–00015) provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund; and Project no. 135784 implemented with the support provided from the National Research, Development and Innovation Fund of Hungary, financed under the K20 funding scheme and the European University for Well-Being (EUniWell) program (grant agreement number: 101004093/EUniWell/EAC-A02-2019/EAC-A02-2019–1). AL and AU were supported by the EKÖP-2024-9 and EKÖP-2024-2, respectively, New National Excellence Program of the Ministry for Culture and Innovation from the Source of the National Research, Development and Innovation Fund. A5 Genetics Ltd (Kutaso, Hungary) provided computational infrastructure for the study. The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the American Heart Association, or the Presbyterian Health Foundation. The 4.0 version of ChatGPT, developed by OpenAI, was used as a language tool to refine our writing and enhancing the clarity of our work.

Declarations

Competing interests Dr. Balázs Győrffy serves as Associate Editor for GeroScience. Dr. Zoltan Ungvari serves as Editor-in-Chief for GeroScience and has personal relationships with individuals involved in the submission of this paper. The authors declare no competing financial interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Hu S, Li Y, Zhu W, Liu J, Wei S. Global, region and national trends and age-period-cohort effects in colorectal cancer burden from 1990 to 2019, with predictions to 2039. Environ Sci Pollut Res Int. 2023;30:83245–59. https://doi.org/10.1007/s11356-023-28223-3.
2. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, Vignat J, Ferlay J, Murphy N, Bray F. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. Gut. 2023;72:338–44. https://doi.org/10.1136/gutjnl-2022-327736.
3. Sharma R. A comparative examination of colorectal cancer burden in European Union, 1990–2019: Estimates from Global Burden of Disease 2019 Study. Int J Clin Oncol. 2022;27:1309–20. https://doi.org/10.1007/s10147-022-02182-0.
4. GBD. Colorectal Cancer Collaborators: Global, regional, and national burden of colorectal cancer and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Gastroenterol Hepatol. 2019;2022(7):627–47. https://doi.org/10.1016/S2468-1253(22)00044-9.
5. Global Burden of Disease Cancer C, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the Global Burden of Disease study. JAMA Oncol. 2019;5:1749-1768. https://doi.org/10.1001/jamaoncol.2019.2996.
6. Fekete M, Major D, Feher A, Fazekas-Pongor V, Lehoczki A. Geroscience and pathology: a new frontier in understanding age-related diseases. Pathol Oncol Res. 2024. https://doi.org/10.3389/pore.2024.1611623.
7. Ungvari Z, Ungvari A, Bianchini G, Gyorffy B. Prognostic significance of a signature based on senescence-related genes in colorectal cancer. Geroscience. 2024. https://doi.org/10.1007/s11357-024-01164-6.
8. Anderson AS, Key TJ, Norat T, Scoccianti C, Cecchini M, Berrino F, Boutron-Ruault MC, Espina C, Leitzmann M, Powers H, et al. European Code against Cancer 4th Edition: obesity, body fatness and cancer. Cancer Epidemiol. 2015;39(Suppl 1):S34-45. https://doi.org/10.1016/j.canep.2015.01.017.
9. Mandic M, Li H, Safizadeh F, Niedermaier T, Hoffmeister M, Brenner H. Is the association of overweight and obesity with colorectal cancer underestimated? An umbrella review of systematic reviews and

meta-analyses. Eur J Epidemiol. 2023;38:135–44. https://doi.org/10.1007/s10654-022-00954-6.
10. Park JY, Mitrou PN, Keogh RH, Luben RN, Wareham NJ, Khaw KT. Self-reported and measured anthropometric data and risk of colorectal cancer in the EPIC-Norfolk study. Int J Obes (Lond). 2012;36:107–18. https://doi.org/10.1038/ijo.2011.61.
11. Matsuo K, Mizoue T, Tanaka K, Tsuji I, Sugawara Y, Sasazuki S, Nagata C, Tamakoshi A, Wakai K, Inoue M. Association between body mass index and the colorectal cancer risk in Japan: pooled analysis of population-based cohort studies in Japan. Ann Oncol. 2012;23:479–90.
12. Hughes LA, Simons CC, van den Brandt PA, Goldbohm RA, van Engeland M, Weijenberg MP. Body size and colorectal cancer risk after 16.3 years of follow-up: an analysis from the Netherlands Cohort Study. Am J Epidemiol. 2011;174:1127–1139. https://doi.org/10.1093/aje/kwr247.
13. Oxentenko AS, Bardia A, Vierkant RA, Wang AH, Anderson KE, Campbell PT, Sellers TA, Folsom AR, Cerhan JR, Limburg PJ. Body size and incident colorectal cancer: a prospective study of older women. Cancer Prev Res (Phila). 2010;3:1608–20. https://doi.org/10.1158/1940-6207.Capr-10-0116.
14. Wang Y, Jacobs EJ, Patel AV, Rodríguez C, McCullough ML, Thun MJ, Calle EE. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. Cancer Causes Control. 2008;19:783–92. https://doi.org/10.1007/s10552-008-9141-x.
15. Wang Y, Jacobs EJ, Teras LR, Pavluck AL, Rodriguez C, Thun MJ, Calle EE. Lack of evidence for effect modification by estrogen of association between body mass index and colorectal cancer risk among postmenopausal women. Cancer Causes Control. 2007;18:793–9. https://doi.org/10.1007/s10552-007-9009-5.
16. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ. 2007;335:1134. https://doi.org/10.1136/bmj.39367.495995.AE.
17. Adams KF, Leitzmann MF, Albanes D, Kipnis V, Mouw T, Hollenbeck A, Schatzkin A. Body mass and colorectal cancer risk in the NIH-AARP cohort. Am J Epidemiol. 2007;166:36–45. https://doi.org/10.1093/aje/kwm049.
18. Lukanova A, Björ O, Kaaks R, Lenner P, Lindahl B, Hallmans G, Stattin P. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. Int J Cancer. 2006;118:458–66. https://doi.org/10.1002/ijc.21354.
19. Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2006;107:28–36.
20. Otani T, Iwasaki M, Inoue M. Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan public health center-based prospective study. Cancer Causes Control. 2005;16:839–50. https://doi.org/10.1007/s10552-005-4573-z.
21. Kuriyama S, Tsubono Y, Hozawa A, Shimazu T, Suzuki Y, Koizumi Y, Suzuki Y, Ohmori K, Nishino Y, Tsuji I. Obesity and risk of cancer in Japan. Int J Cancer. 2005;113:148–57. https://doi.org/10.1002/ijc.20529.
22. Engeland A, Tretli S, Austad G, Bjørge T. Height and body mass index in relation to colorectal and gallbladder cancer in two million Norwegian men and women. Cancer Causes Control. 2005;16:987–96. https://doi.org/10.1007/s10552-005-3638-3.
23. Lin J, Zhang SM, Cook NR, Rexrode KM, Lee IM, Buring JE. Body mass index and risk of colorectal cancer in women (United States). Cancer Causes Control. 2004;15:581–9. https://doi.org/10.1023/B:CACO.0000036168.23351.f1.
24. Terry PD, Miller AB, Rohan TE. Obesity and colorectal cancer risk in women. Gut. 2002;51:191–4. https://doi.org/10.1136/gut.51.2.191.
25. Terry P, Giovannucci E, Bergkvist L, Holmberg L, Wolk A. Body weight and colorectal cancer risk in a cohort of Swedish women: relation varies by age and cancer site. Br J Cancer. 2001;85:346–9. https://doi.org/10.1054/bjoc.2001.1894.
26. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, Rinaldi S, Zeleniuch-Jacquotte A, Shore RE, Riboli E. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst. 2000;92:1592–600.
27. Bassett JK, Severi G, English DR, Baglietto L, Krishnan K, Hopper JL, Giles GG. Body size, weight change, and risk of colon cancer. Cancer Epidemiol Biomarkers Prev. 2010;19:2978–86. https://doi.org/10.1158/1055-9965.Epi-10-0543.
28. Han X, Stevens J, Truesdale KP, Bradshaw PT, Kucharska-Newton A, Prizment AE, Platz EA, Joshu CE. Body mass index at early adulthood, subsequent weight change and cancer incidence and mortality. Int J Cancer. 2014;135:2900–9. https://doi.org/10.1002/ijc.28930.
29. Elangovan A, Skeans J, Landsman M, Ali SMJ, Elangovan AG, Kaelber DC, Sandhu DS, Cooper GS. Colorectal cancer, age, and obesity-related comorbidities: a large database study. Dig Dis Sci. 2021;66:3156–63. https://doi.org/10.1007/s10620-020-06602-x.
30. Noh H, Charvat H, Freisling H, Ólafsdóttir GH, Ólafsdóttir EJ, Tryggvadóttir L, Arnold M, Soerjomataram I. Cumulative exposure to premenopausal obesity and risk of postmenopausal cancer: a population-based study in Icelandic women. Int J Cancer. 2020;147:793–802. https://doi.org/10.1002/ijc.32805.
31. Zhang X, Wu K, Giovannucci EL, Ma J, Colditz GA, Fuchs CS, Willett WC, Stampfer MJ, Nimptsch K, Ogino S, Wei EK. Early life body fatness and risk of colorectal cancer in U.S. women and men-results from two large cohort studies. Cancer Epidemiol Biomarkers Prev. 2015;24:690–697. https://doi.org/10.1158/1055-9965.Epi-14-0909-t.
32. Levi Z, Kark JD, Katz LH, Twig G, Derazne E, Tzur D, Leibovici Weissman Y, Leiba A, Lipshiez I, Keinan Boker L, Afek A. Adolescent body mass index and risk of colon and rectal cancer in a cohort of 1.79 million Israeli men and women: a population-based study.

Cancer. 2017;123:4022–4030. https://doi.org/10.1002/cncr.30819.
33. Kantor ED, Udumyan R, Signorello LB, Giovannucci EL, Montgomery S, Fall K. Adolescent body mass index and erythrocyte sedimentation rate in relation to colorectal cancer risk. Gut. 2016;65:1289–95. https://doi.org/10.1136/gutjnl-2014-309007.
34. Lee IM, Paffenbarger RS Jr. Quetelet's index and risk of colon cancer in college alumni. J Natl Cancer Inst. 1992;84:1326–31. https://doi.org/10.1093/jnci/84.17.1326.
35. Larsson SC, Rutegård J, Bergkvist L, Wolk A. Physical activity, obesity, and risk of colon and rectal cancer in a cohort of Swedish men. Eur J Cancer. 2006;42:2590–7. https://doi.org/10.1016/j.ejca.2006.04.015.
36. Bowers K, Albanes D, Limburg P, Pietinen P, Taylor PR, Virtamo J, Stolzenberg-Solomon R. A prospective study of anthropometric and clinical measurements associated with insulin resistance syndrome and colorectal cancer in male smokers. Am J Epidemiol. 2006;164:652–64. https://doi.org/10.1093/aje/kwj253.
37. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, Dobs A, Savage PJ. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst. 1999;91:1147–54. https://doi.org/10.1093/jnci/91.13.1147.
38. Moore LL, Bradlee ML, Singer MR, Splansky GL, Proctor MH, Ellison RC, Kreger BE. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes Relat Metab Disord. 2004;28:559–67. https://doi.org/10.1038/sj.ijo.0802606.
39. Driver JA, Gaziano JM, Gelber RP, Lee I-M, Buring JE, Kurth T. Development of a risk score for colorectal cancer in men. Am J Med. 2007;120:257–63.
40. Odegaard AO, Koh WP, Yu MC, Yuan JM. Body mass index and risk of colorectal cancer in Chinese Singaporeans: the Singapore Chinese Health Study. Cancer. 2011;117:3841–9. https://doi.org/10.1002/cncr.25936.
41. Glover M, Mansoor E, Panhwar M, Parasa S, Cooper GS. Epidemiology of colorectal cancer in average risk adults 20–39 years of age: a population-based national study. Dig Dis Sci. 2019;64:3602–9. https://doi.org/10.1007/s10620-019-05690-8.
42. Liu PH, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, He X, Fuchs CS, Ogino S, Willett WC, et al. Association of obesity with risk of early-onset colorectal cancer among women. JAMA Oncol. 2019;5:37–44. https://doi.org/10.1001/jamaoncol.2018.4280.
43. Syed AR, Thakkar P, Horne ZD, Abdul-Baki H, Kochhar G, Farah K, Thakkar S. Old vs new: risk factors predicting early onset colorectal cancer. World J Gastrointest Oncol. 2019;11:1011–20. https://doi.org/10.4251/wjgo.v11.i11.1011.
44. Dash C, Yu J, Nomura S, Lu J, Rosenberg L, Palmer JR, Adams-Campbell LL. Obesity is an initiator of colon adenomas but not a promoter of colorectal cancer in the Black Women's Health Study. Cancer Causes Control. 2020;31:291–302. https://doi.org/10.1007/s10552-020-01283-3.
45. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. Lancet. 2014;384:755–765. https://doi.org/10.1016/s0140-6736(14)60892-8.
46. Lu Y, Ness-Jensen E, Hveem K, Martling A. Metabolic predispositions and increased risk of colorectal adenocarcinoma by anatomical location: a large population-based cohort study in Norway. Am J Epidemiol. 2015;182:883–93. https://doi.org/10.1093/aje/kwv141.
47. Hanyuda A, Cao Y, Hamada T, Nowak JA, Qian ZR, Masugi Y, da Silva A, Liu L, Kosumi K, Soong TR, et al. Body mass index and risk of colorectal carcinoma subtypes classified by tumor differentiation status. Eur J Epidemiol. 2017;32:393–407. https://doi.org/10.1007/s10654-017-0254-y.
48. Wang L, Jin G, Yu C, Lv J, Guo Y, Bian Z, Yang L, Chen Y, Hu Z, Chen F, et al. Cancer incidence in relation to body fatness among 0.5 million men and women: findings from the China Kadoorie Biobank. Int J Cancer. 2020;146:987–998. https://doi.org/10.1002/ijc.32394.
49. Bjørge T, Häggström C, Ghaderi S, Nagel G, Manjer J, Tretli S, Ulmer H, Harlid S, Rosendahl AH, Lang A, et al. BMI and weight changes and risk of obesity-related cancers: a pooled European cohort study. Int J Epidemiol. 2019;48:1872–85. https://doi.org/10.1093/ije/dyz188.
50. Doubeni CA, Laiyemo AO, Major JM, Schootman M, Lian M, Park Y, Graubard BI, Hollenbeck AR, Sinha R. Socioeconomic status and the risk of colorectal cancer: an analysis of more than a half million adults in the National Institutes of Health-AARP Diet and Health Study. Cancer. 2012;118:3636–44. https://doi.org/10.1002/cncr.26677.
51. Rapp K, Klenk J, Ulmer H, Concin H, Diem G, Oberaigner W, Schroeder J. Weight change and cancer risk in a cohort of more than 65,000 adults in Austria. Ann Oncol. 2008;19:641–8. https://doi.org/10.1093/annonc/mdm549.
52. Song YM, Sung J, Ha M. Obesity and risk of cancer in postmenopausal Korean women. J Clin Oncol. 2008;26:3395–402. https://doi.org/10.1200/jco.2007.15.7867.
53. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol. 2005;23:4742–54. https://doi.org/10.1200/jco.2005.11.726.
54. Laake I, Thune I, Selmer R, Tretli S, Slattery ML, Veierød MB. A prospective study of body mass index, weight change, and risk of cancer in the proximal and distal colon. Cancer Epidemiol Biomarkers Prev. 2010;19:1511–22. https://doi.org/10.1158/1055-9965.Epi-09-0813.
55. Renehan AG, Flood A, Adams KF, Olden M, Hollenbeck AR, Cross AJ, Leitzmann MF. Body mass index at different adult ages, weight change, and colorectal cancer risk in the National Institutes of Health-AARP Cohort. Am J Epidemiol. 2012;176:1130–40. https://doi.org/10.1093/aje/kws192.

56. Li H, Yang G, Xiang YB, Zhang X, Zheng W, Gao YT, Shu XO. Body weight, fat distribution and colorectal cancer risk: a report from cohort studies of 134255 Chinese men and women. Int J Obes (Lond). 2013;37:783–9. https://doi.org/10.1038/ijo.2012.152.
57. Steins Bisschop CN, van Gils CH, Emaus MJ, Bueno-de-Mesquita HB, Monninkhof EM, Boeing H, Aleksandrova K, Jenab M, Norat T, Riboli E, et al. Weight change later in life and colon and rectal cancer risk in participants in the EPIC-PANACEA study. Am J Clin Nutr. 2014;99:139–47. https://doi.org/10.3945/ajcn.113.066530.
58. Andreasson A, Hagström H, Sköldberg F, Önnerhag K, Carlsson AC, Schmidt PT, Forsberg AM. The prediction of colorectal cancer using anthropometric measures: a Swedish population-based cohort study with 22 years of follow-up. United European Gastroenterol J. 2019;7:1250–60. https://doi.org/10.1177/2050640619854278.
59. Sanford NN, Giovannucci EL, Ahn C, Dee EC, Mahal BA. Obesity and younger versus older onset colorectal cancer in the United States, 1998–2017. J Gastrointest Oncol. 2020;11:121–6. https://doi.org/10.21037/jgo.2019.12.07.
60. Saeed U, Myklebust T, Robsahm TE, Kielland MF, Møller B, Skålhegg BS, Mala T, Yaqub S. Risk and survival in colorectal cancer with increasing body mass index: A nationwide population-based cohort study. Colorectal Dis. 2023;25:375–85. https://doi.org/10.1111/codi.16367.
61. Wang SY, Zhang WS, Jiang CQ, Jin YL, Zhu T, Zhu F, Xu L. Association of novel and conventional obesity indices with colorectal cancer risk in older Chinese: a 14-year follow-up of the Guangzhou Biobank Cohort Study. BMC Cancer. 2023;23:286. https://doi.org/10.1186/s12885-023-10762-0.
62. Caan BJ, Coates AO, Slattery ML, Potter JD, Quesenberry CP Jr, Edwards SM. Body size and the risk of colon cancer in a large case-control study. Int J Obes Relat Metab Disord. 1998;22:178–84. https://doi.org/10.1038/sj.ijo.0800561.
63. Russo A, Franceschi S, La Vecchia C, Dal Maso L, Montella M, Conti E, Giacosa A, Falcini F, Negri E. Body size and colorectal-cancer risk. Int J Cancer. 1998;78:161–5. https://doi.org/10.1002/(sici)1097-0215(19981005)78:2%3c161::aid-ijc7%3e3.0.co;2-x.
64. Hou L, Ji BT, Blair A, Dai Q, Gao YT, Potter JD, Chow WH. Body mass index and colon cancer risk in Chinese people: menopause as an effect modifier. Eur J Cancer. 2006;42:84–90. https://doi.org/10.1016/j.ejca.2005.09.014.
65. Campbell PT, Cotterchio M, Dicks E, Parfrey P, Gallinger S, McLaughlin JR. Excess body weight and colorectal cancer risk in Canada: associations in subgroups of clinically defined familial risk of cancer. Cancer Epidemiol Biomarkers Prev. 2007;16:1735–44. https://doi.org/10.1158/1055-9965.Epi-06-1059.
66. Nock NL, Thompson CL, Tucker TC, Berger NA, Li L. Associations between obesity and changes in adult BMI over time and colon cancer risk. Obesity (Silver Spring). 2008;16:1099–104. https://doi.org/10.1038/oby.2008.42.
67. Campbell PT, Jacobs ET, Ulrich CM, Figueiredo JC, Poynter JN, McLaughlin JR, Haile RW, Jacobs EJ, Newcomb PA, Potter JD, et al. Case-control study of overweight, obesity, and colorectal cancer risk, overall and by tumor microsatellite instability status. J Natl Cancer Inst. 2010;102:391–400. https://doi.org/10.1093/jnci/djq011.
68. Blake-Gumbs L, Chen Z, Thompson CL, Berger NA, Tucker TC, Li L. Adult BMI change and risk of colon cancer in postmenopausal women. J Obes. 2012;2012:857510. https://doi.org/10.1155/2012/857510.
69. Rosato V, Bosetti C, Levi F, Polesel J, Zucchetto A, Negri E, La Vecchia C. Risk factors for young-onset colorectal cancer. Cancer Causes Control. 2013;24:335–41. https://doi.org/10.1007/s10552-012-0119-3.
70. Boyle T, Fritschi L, Tabatabaei SM, Ringwald K, Heyworth JS. Smoking, alcohol, diabetes, obesity, socioeconomic status, and the risk of colorectal cancer in a population-based case-control study. Cancer Causes Control. 2014;25:1659–68. https://doi.org/10.1007/s10552-014-0470-7.
71. Gausman V, Dornblaser D, Anand S, Hayes RB, O'Connell K, Du M, Liang PS. Risk factors associated with early-onset colorectal cancer. Clin Gastroenterol Hepatol. 2020;18:2752-2759.e2752. https://doi.org/10.1016/j.cgh.2019.10.009.
72. Low EE, Demb J, Liu L, Earles A, Bustamante R, Williams CD, Provenzale D, Kaltenbach T, Gawron AJ, Martinez ME, Gupta S. Risk factors for early-onset colorectal cancer. Gastroenterology. 2020;159:492-501.e497. https://doi.org/10.1053/j.gastro.2020.01.004.
73. Schumacher AJ, Chen Q, Attaluri V, McLemore EC, Chao CR. Metabolic risk factors associated with early-onset colorectal adenocarcinoma: a case-control study at Kaiser Permanente Southern California. Cancer Epidemiol Biomarkers Prev. 2021;30:1792–8. https://doi.org/10.1158/1055-9965.Epi-20-1127.
74. Li H, Boakye D, Chen X, Jansen L, Chang-Claude J, Hoffmeister M, Brenner H. Associations of body mass index at different ages with early-onset colorectal cancer. Gastroenterology. 2022;162:1088-1097.e1083. https://doi.org/10.1053/j.gastro.2021.12.239.
75. Loomans-Kropp HA, Umar A. Analysis of body mass index in early and middle adulthood and estimated risk of gastrointestinal cancer. JAMA Netw Open. 2023;6:e2310002. https://doi.org/10.1001/jamanetworkopen.2023.10002.
76. Meulmeester FL, Willems van Dijk K, Mooijaart SP, van Heemst D, Noordam R. The association of measures of body shape and adiposity with incidence of cardiometabolic disease from an ageing perspective. Geroscience. 2023;45:463–476. https://doi.org/10.1007/s11357-022-00654-9.
77. Temple NJ, Conklin A. Prevalence of overweight and obesity in Western countries: discrepancies in published estimates. Eur J Epidemiol. 2019;34:711–3. https://doi.org/10.1007/s10654-019-00503-8.
78. EUROSTAT: Overweight and obesity - BMI statistics. https://ec.europa.eu/eurostat/statistics-explained/index.

php?title=Overweight_and_obesity_-_BMI_statistics acccessed on 06/29/2024.
79. Wang YC, Colditz GA, Kuntz KM. Forecasting the obesity epidemic in the aging U.S. population. Obesity (Silver Spring). 2007;15:2855–2865. https://doi.org/10.1038/oby.2007.339.
80. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA. 2012;307:491–7. https://doi.org/10.1001/jama.2012.39.
81. Ogden CL, Fryar CD, Martin CB, Freedman DS, Carroll MD, Gu Q, Hales CM. Trends in obesity prevalence by race and Hispanic origin—1999-2000 to 2017–2018. JAMA. 2020;324:1208–10. https://doi.org/10.1001/jama.2020.14590.
82. Fang M, Echouffo-Tcheugui JB, Selvin E. Prevalence and management of obesity in U.S. adults with type 1 diabetes. Ann Intern Med. 2023;176:eL230228. https://doi.org/10.7326/L23-0228.
83. Ellison-Barnes A, Johnson S, Gudzune K. Trends in obesity prevalence among adults aged 18 through 25 years, 1976–2018. JAMA. 2021;326:2073–4. https://doi.org/10.1001/jama.2021.16685.
84. Salerno P, Qian A, Dong W, Deo S, Nasir K, Rajagopalan S, Al-Kindi S. County-level socio-environmental factors and obesity prevalence in the United States. Diabetes Obes Metab. 2024;26:1766–74. https://doi.org/10.1111/dom.15488.
85. Cao X, Wang M, Zhou M, Mi Y, Fazekas-Pongor V, Major D, Lehoczki A, Guo Y. Trends in prevalence, mortality, and risk factors of dementia among the oldest-old adults in the United States: the role of the obesity epidemic. Geroscience. 2024. https://doi.org/10.1007/s11357-024-01180-6.
86. Valcarcel-Ares MN, Tucsek Z, Kiss T, Giles CB, Tarantini S, Yabluchanskiy A, Balasubramanian P, Gautam T, Galvan V, Ballabh P, et al. Obesity in aging exacerbates neuroinflammation, dysregulating synaptic function-related genes and altering eicosanoid synthesis in the mouse hippocampus: potential role in impaired synaptic plasticity and cognitive decline. J Gerontol A Biol Sci Med Sci. 2018. https://doi.org/10.1093/gerona/gly127.
87. Tucsek Z, Toth P, Tarantini S, Sosnowska D, Gautam T, Warrington JP, Giles CB, Wren JD, Koller A, Ballabh P, et al. Aging exacerbates obesity-induced cerebromicrovascular rarefaction, neurovascular uncoupling, and cognitive decline in mice. J Gerontol A Biol Sci Med Sci. 2014;69:1339–52. https://doi.org/10.1093/gerona/glu080.
88. Tucsek Z, Toth P, Sosnowska D, Gautam T, Mitschelen M, Koller A, Szalai G, Sonntag WE, Ungvari Z, Csiszar A. Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. J Gerontol A Biol Sci Med Sci. 2014;69:1212–26. https://doi.org/10.1093/gerona/glt177.
89. Schachtschneider KM, Schook LB, Meudt JJ, Shanmuganayagam D, Zoller JA, Haghani A, Li CZ, Zhang J, Yang A, Raj K, Horvath S. Epigenetic clock and DNA methylation analysis of porcine models of aging and obesity. Geroscience. 2021;43:2467–83. https://doi.org/10.1007/s11357-021-00439-6.
90. Samara A, Murphy T, Strain J, Rutlin J, Sun P, Neyman O, Sreevalsan N, Shimony JS, Ances BM, Song SK, et al. Neuroinflammation and white matter alterations in obesity assessed by diffusion basis spectrum imaging. Front Hum Neurosci. 2019;13:464. https://doi.org/10.3389/fnhum.2019.00464.
91. Horvath S, Erhart W, Brosch M, Ammerpohl O, von Schonfels W, Ahrens M, Heits N, Bell JT, Tsai PC, Spector TD, et al. Obesity accelerates epigenetic aging of human liver. Proc Natl Acad Sci U S A. 2014;111:15538–43. https://doi.org/10.1073/pnas.1412759111.
92. Ganguli M, Beer JC, Zmuda JM, Ryan CM, Sullivan KJ, Chang CH, Rao RH. Aging, diabetes, obesity, and cognitive decline: a population-based study. J Am Geriatr Soc. 2020. https://doi.org/10.1111/jgs.16321.
93. Dearborn JL, Schneider AL, Sharrett AR, Mosley TH, Bezerra DC, Knopman DS, Selvin E, Jack CR, Coker LH, Alonso A, et al. Obesity, insulin resistance, and incident small vessel disease on magnetic resonance imaging: atherosclerosis risk in communities study. Stroke. 2015;46:3131–6. https://doi.org/10.1161/STROKEAHA.115.010060.
94. Dake MD, De Marco M, Blackburn DJ, Wilkinson ID, Remes A, Liu Y, Pikkarainen M, Hallikainen M, Soininen H, Venneri A. Obesity and brain vulnerability in normal and abnormal aging: a multimodal MRI study. J Alzheimers Dis Rep. 2021;5:65–77. https://doi.org/10.3233/ADR-200267.
95. Dahl AK, Hassing LB. Obesity and cognitive aging. Epidemiol Rev. 2013;35:22–32. https://doi.org/10.1093/epirev/mxs002.
96. Caunca MR, Gardener H, Simonetto M, Cheung YK, Alperin N, Yoshita M, DeCarli C, Elkind MSV, Sacco RL, Wright CB, Rundek T. Measures of obesity are associated with MRI markers of brain aging: the Northern Manhattan Study. Neurology. 2019;93:e791–803. https://doi.org/10.1212/WNL.0000000000007966.
97. Wu D, Ren Z, Pae M, Guo W, Cui X, Merrill AH, Meydani SN. Aging up-regulates expression of inflammatory mediators in mouse adipose tissue. J Immunol. 2007;179:4829–39.
98. Bailey-Downs LC, Tucsek Z, Toth P, Sosnowska D, Gautam T, Sonntag WE, Csiszar A, Ungvari Z. Aging exacerbates obesity-induced oxidative stress and inflammation in perivascular adipose tissue in mice: a paracrine mechanism contributing to vascular redox dysregulation and inflammation. J Gerontol A Biol Sci Med Sci. 2013;68:780–92. https://doi.org/10.1093/gerona/gls238.
99. Thomas AL, Alarcon PC, Divanovic S, Chougnet CA, Hildeman DA, Moreno-Fernandez ME. Implications of inflammatory states on dysfunctional immune responses in aging and obesity. Front Aging. 2021;2:732414. https://doi.org/10.3389/fragi.2021.732414.
100. Santos AL, Sinha S. Obesity and aging: Molecular mechanisms and therapeutic approaches. Ageing Res Rev. 2021;67:101268. https://doi.org/10.1016/j.arr.2021.101268.

101. Canugovi C, Stevenson MD, Vendrov AE, Hayami T, Robidoux J, Xiao H, Zhang YY, Eitzman DT, Runge MS, Madamanchi NR. Increased mitochondrial NADPH oxidase 4 (NOX4) expression in aging is a causative factor in aortic stiffening. Redox Biol. 2019;26:101288. https://doi.org/10.1016/j.redox.2019.101288.
102. Burton DGA, Faragher RGA. Obesity and type-2 diabetes as inducers of premature cellular senescence and ageing. Biogerontology. 2018;19:447–59. https://doi.org/10.1007/s10522-018-9763-7.
103. Balasubramanian P, Kiss T, Tarantini S, Nyul-Toth A, Ahire C, Yabluchanskiy A, Csipo T, Lipecz A, Tabak A, Institoris A, et al. Obesity-induced cognitive impairment in older adults: a microvascular perspective. Am J Physiol Heart Circ Physiol. 2021;320:H740–61. https://doi.org/10.1152/ajpheart.00736.2020.
104. Lega IC, Lipscombe LL. Review: diabetes, obesity, and cancer-pathophysiology and clinical implications. Endocr Rev. 2020;41. https://doi.org/10.1210/endrev/bnz014.
105. Jones AN, Scheurlen KM, Macleod A, Simon HL, Galandiuk S. Obesity and inflammatory factors in the progression of early-onset colorectal cancer. Cancers (Basel). 2024;16. https://doi.org/10.3390/cancers16071403.
106. Harris BHL, Macaulay VM, Harris DA, Klenerman P, Karpe F, Lord SR, Harris AL, Buffa FM. Obesity: a perfect storm for carcinogenesis. Cancer Metastasis Rev. 2022;41:491–515. https://doi.org/10.1007/s10555-022-10046-2.
107. Nunan E, Wright CL, Semola OA, Subramanian M, Balasubramanian P, Lovern PC, Fancher IS, Butcher JT. Obesity as a premature aging phenotype - implications for sarcopenic obesity. Geroscience. 2022;44:1393–405. https://doi.org/10.1007/s11357-022-00567-7.
108. Murphy N, Newton CC, Song M, Papadimitriou N, Hoffmeister M, Phipps AI, Harrison TA, Newcomb PA, Aglago EK, Berndt SI, et al. Body mass index and molecular subtypes of colorectal cancer. J Natl Cancer Inst. 2023;115:165–73. https://doi.org/10.1093/jnci/djac215.
109. Kant P, Hull MA. Excess body weight and obesity–the link with gastrointestinal and hepatobiliary cancer. Nat Rev Gastroenterol Hepatol. 2011;8:224–38. https://doi.org/10.1038/nrgastro.2011.23.
110. Ahechu P, Zozaya G, Marti P, Hernandez-Lizoain JL, Baixauli J, Unamuno X, Fruhbeck G, Catalan V. NLRP3 inflammasome: a possible link between obesity-associated low-grade chronic inflammation and colorectal cancer development. Front Immunol. 2018;9:2918. https://doi.org/10.3389/fimmu.2018.02918.
111. Meier HCS, Mitchell C, Karadimas T, Faul JD. Systemic inflammation and biological aging in the Health and Retirement Study. Geroscience. 2023;45:3257–65. https://doi.org/10.1007/s11357-023-00880-9.
112. Bruno MEC, Mukherjee S, Powell WL, Mori SF, Wallace FK, Balasuriya BK, Su LC, Stromberg AJ, Cohen DA, Starr ME. Accumulation of γδ T cells in visceral fat with aging promotes chronic inflammation. Geroscience. 2022;44:1761–78. https://doi.org/10.1007/s11357-022-00572-w.
113. Hammoud SH, AlZaim I, Al-Dhaheri Y, Eid AH, El-Yazbi AF. Perirenal adipose tissue inflammation: novel insights linking metabolic dysfunction to renal diseases. Front Endocrinol (Lausanne). 2021;12:707126. https://doi.org/10.3389/fendo.2021.707126.
114. Weisberg SP, Hunter D, Huber R, Lemieux J, Slaymaker S, Vaddi K, Charo I, Leibel RL, Ferrante AW Jr. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. J Clin Invest. 2006;116:115–24. https://doi.org/10.1172/JCI24335.
115. Verhagen SN, Visseren FL. Perivascular adipose tissue as a cause of atherosclerosis. Atherosclerosis. 2011;214:3–10. https://doi.org/10.1016/j.atherosclerosis.2010.05.034.
116. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM, Dixit VD. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med. 2011;17:179–88. https://doi.org/10.1038/nm.2279.
117. Surmi BK, Hasty AH. Macrophage infiltration into adipose tissue: initiation, propagation and remodeling. Future Lipidol. 2008;3:545–56. https://doi.org/10.2217/17460875.3.5.545.
118. Stranahan AM. Visceral adiposity, inflammation, and hippocampal function in obesity. Neuropharmacology. 2022;205:108920. https://doi.org/10.1016/j.neuropharm.2021.108920.
119. Palmer AK, Xu M, Zhu Y, Pirtskhalava T, Weivoda MM, Hachfeld CM, Prata LG, van Dijk TH, Verkade E, Casaclang-Verzosa G, et al. Targeting senescent cells alleviates obesity-induced metabolic dysfunction. Aging Cell. 2019;18:e12950. https://doi.org/10.1111/acel.12950.
120. Nishimura S, Manabe I, Nagasaki M, Seo K, Yamashita H, Hosoya Y, Ohsugi M, Tobe K, Kadowaki T, Nagai R, Sugiura S. In vivo imaging in mice reveals local cell dynamics and inflammation in obese adipose tissue. J Clin Invest. 2008;118:710–21. https://doi.org/10.1172/JCI33328.
121. Maachi M, Pieroni L, Bruckert E, Jardel C, Fellahi S, Hainque B, Capeau J, Bastard JP. Systemic low-grade inflammation is related to both circulating and adipose tissue TNFα, leptin and IL-6 levels in obese women. Int J Obes Relat Metab Disord. 2004;28:993–7. https://doi.org/10.1038/sj.ijo.0802718.
122. Matacchione G, Perugini J, Di Mercurio E, Sabbatinelli J, Prattichizzo F, Senzacqua M, Storci G, Dani C, Lezoche G, Guerrieri M, et al. Senescent macrophages in the human adipose tissue as a source of inflammaging. Geroscience. 2022;44:1941–60. https://doi.org/10.1007/s11357-022-00536-0.
123. Zhang H, Zhang C. Regulation of microvascular function by adipose tissue in obesity and type 2 diabetes: evidence of an adipose-vascular loop. Am J Biomed Sci. 2009;1:133–42.
124. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112:1821–30. https://doi.org/10.1172/JCI19451.
125. Police SB, Thatcher SE, Charnigo R, Daugherty A, Cassis LA. Obesity promotes inflammation in periaortic adipose tissue and angiotensin II-induced abdominal aortic

aneurysm formation. Arterioscler Thromb Vasc Biol. 2009;29:1458–64. https://doi.org/10.1161/ATVBAHA.109.192658.
126. Misiak B, Leszek J, Kiejna A. Metabolic syndrome, mild cognitive impairment and Alzheimer's disease–the emerging role of systemic low-grade inflammation and adiposity. Brain Res Bull. 2012;89:144–9. https://doi.org/10.1016/j.brainresbull.2012.08.003.
127. Knight EM, Martins IV, Gumusgoz S, Allan SM, Lawrence CB. High-fat diet-induced memory impairment in triple-transgenic Alzheimer's disease (3xTgAD) mice is independent of changes in amyloid and tau pathology. Neurobiol Aging. 2014;35:1821–32. https://doi.org/10.1016/j.neurobiolaging.2014.02.010.
128. Henrichot E, Juge-Aubry CE, Pernin A, Pache JC, Velebit V, Dayer JM, Meda P, Chizzolini C, Meier CA. Production of chemokines by perivascular adipose tissue: a role in the pathogenesis of atherosclerosis? Arterioscler Thromb Vasc Biol. 2005;25:2594–9. https://doi.org/10.1161/01.ATV.0000188508.40052.35.
129. Fantuzzi G, Mazzone T. Adipose tissue and atherosclerosis: exploring the connection. Arterioscler Thromb Vasc Biol. 2007;27:996–1003. https://doi.org/10.1161/ATVBAHA.106.131755.
130. Erion JR, Wosiski-Kuhn M, Dey A, Hao S, Davis CL, Pollock NK, Stranahan AM. Obesity elicits interleukin 1-mediated deficits in hippocampal synaptic plasticity. J Neurosci. 2014;34:2618–31. https://doi.org/10.1523/JNEUROSCI.4200-13.2014.
131. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444:881–7.
132. Bunnell BA, Martin EC, Matossian MD, Brock CK, Nguyen K, Collins-Burow B, Burow ME. The effect of obesity on adipose-derived stromal cells and adipose tissue and their impact on cancer. Cancer Metastasis Rev. 2022;41:549–73. https://doi.org/10.1007/s10555-022-10063-1.
133. Strong AL, Burow ME, Gimble JM, Bunnell BA. Concise review: The obesity cancer paradigm: exploration of the interactions and crosstalk with adipose stem cells. Stem Cells. 2015;33:318–26. https://doi.org/10.1002/stem.1857.
134. Hamada K, Kubota Y, Aoki Y, Sugisawa N, Yamamoto J, Tashiro Y, Bouvet M, Tsunoda T, Hoffman RM. Obesity strongly promotes growth of mouse MC38 colon cancer in an orthotopic-syngeneic C57BL/6 mouse model. In Vivo. 2022;36:1643–6. https://doi.org/10.21873/invivo.12875.
135. Moon SG, Park B. The association between metabolic syndrome and colorectal cancer risk by obesity status in Korean women: a nationwide cohort study. J Prev Med Public Health. 2022;55:475–84. https://doi.org/10.3961/jpmph.22.286.
136. Jung SY, Barrington WE, Lane DS, Chen C, Chlebowski R, Corbie-Smith G, Hou L, Zhang ZF, Paek MS, Crandall CJ. Bioavailable insulin-like growth factor-I as mediator of racial disparity in obesity-relevant breast and colorectal cancer risk among postmenopausal women. Menopause. 2017;24:288–98. https://doi.org/10.1097/GME.0000000000000753.
137. Berryman DE, Glad CA, List EO, Johannsson G. The GH/IGF-1 axis in obesity: pathophysiology and therapeutic considerations. Nat Rev Endocrinol. 2013;9:346–56. https://doi.org/10.1038/nrendo.2013.64.
138. Socol CT, Chira A, Martinez-Sanchez MA, Nunez-Sanchez MA, Maerescu CM, Mierlita D, Rusu AV, Ruiz-Alcaraz AJ, Trif M, Ramos-Molina B. Leptin signaling in obesity and colorectal cancer. Int J Mol Sci. 2022;23. https://doi.org/10.3390/ijms23094713.
139. Riondino S, Roselli M, Palmirotta R, Della-Morte D, Ferroni P, Guadagni F. Obesity and colorectal cancer: role of adipokines in tumor initiation and progression. World J Gastroenterol. 2014;20:5177–90. https://doi.org/10.3748/wjg.v20.i18.5177.
140. Taguri M, Kuchiba A, Yamaji T, Sawada N, Goto A, Iwasaki M, Tsugane S. Importance of circulating leptin and adiponectin in the causal pathways between obesity and the development of colorectal cancer in Japanese men. J Epidemiol. 2024. https://doi.org/10.2188/jea.JE20230148.
141. Stattin P, Lukanova A, Biessy C, Soderberg S, Palmqvist R, Kaaks R, Olsson T, Jellum E. Obesity and colon cancer: does leptin provide a link? Int J Cancer. 2004;109:149–52. https://doi.org/10.1002/ijc.11668.
142. Koda M, Sulkowska M, Kanczuga-Koda L, Surmacz E, Sulkowski S. Overexpression of the obesity hormone leptin in human colorectal cancer. J Clin Pathol. 2007;60:902–6. https://doi.org/10.1136/jcp.2006.041004.
143. Chen YC, Chien CY, Hsu CC, Lee CH, Chou YT, Shiah SG, Liu SY, Yen CY, Hsieh AC, Wabitsch M, Shieh YS. Obesity-associated leptin promotes chemoresistance in colorectal cancer through YAP-dependent AXL upregulation. Am J Cancer Res. 2021;11:4220–40.
144. Caruso A, Gelsomino L, Panza S, Accattatis FM, Naimo GD, Barone I, Giordano C, Catalano S, Ando S. Leptin: A Heavyweight Player in Obesity-Related Cancers. Biomolecules. 2023;13. https://doi.org/10.3390/biom13071084.
145. Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: role in cancer promotion. Horm Mol Biol Clin Investig. 2015;21:57–74. https://doi.org/10.1515/hmbci-2014-0037.
146. Tumminia A, Vinciguerra F, Parisi M, Graziano M, Sciacca L, Baratta R, Frittitta L. Adipose tissue, obesity and adiponectin: role in endocrine cancer risk. Int J Mol Sci. 2019;20. https://doi.org/10.3390/ijms20122863.
147. Li J, Chen Z, Wang Q, Du L, Yang Y, Guo F, Li X, Chao Y, Ma Y. Microbial and metabolic profiles unveil mutualistic microbe-microbe interaction in obesity-related colorectal cancer. Cell Rep Med. 2024;5:101429. https://doi.org/10.1016/j.xcrm.2024.101429.
148. Zafari N, Velayati M, Mehrabadi S, Damavandi S, Khazaei M, Hassanian SM, Ferns GA, Avan A. Remodeling of the gut microbiota in colorectal cancer and its association with obesity. Curr Pharm Des. 2023;29:256–71. https://doi.org/10.2174/1381612829666230118123018.
149. McLeod A, Wolf P, Chapkin RS, Davidson LA, Ivanov I, Berbaum M, Williams LR, Gaskins HR, Ridlon J, Sanchez-Flack J, et al. Design of the Building Research in CRC prevention (BRIDGE-CRC) trial: a 6-month,

parallel group Mediterranean diet and weight loss randomized controlled lifestyle intervention targeting the bile acid-gut microbiome axis to reduce colorectal cancer risk among African American/Black adults with obesity. Trials. 2023;24:113. https://doi.org/10.1186/s13063-023-07115-4.
150. Greathouse KL, White JR, Padgett RN, Perrotta BG, Jenkins GD, Chia N, Chen J. Gut microbiome meta-analysis reveals dysbiosis is independent of body mass index in predicting risk of obesity-associated CRC. BMJ Open Gastroenterol. 2019;6:e000247. https://doi.org/10.1136/bmjgast-2018-000247.
151. Milner JJ, Chen ZF, Grayson J, Shiao SPK. Obesity-associated differentially methylated regions in colon cancer. J Pers Med. 2022;12. https://doi.org/10.3390/jpm12050660.
152. Bultman SJ. A reversible epigenetic link between obesity and cancer risk. Trends Endocrinol Metab. 2018;29:529–31. https://doi.org/10.1016/j.tem.2018.05.004.
153. Ayers D, Boughanem H, Macias-Gonzalez M. Epigenetic influences in the obesity/colorectal cancer axis: a novel theragnostic avenue. J Oncol. 2019;2019:7406078. https://doi.org/10.1155/2019/7406078.
154. Tait S, Baldassarre A, Masotti A, Calura E, Martini P, Vari R, Scazzocchio B, Gessani S, Del Corno M. Integrated transcriptome analysis of human visceral adipocytes unravels dysregulated microRNA-long non-coding RNA-mRNA networks in obesity and colorectal cancer. Front Oncol. 2020;10:1089. https://doi.org/10.3389/fonc.2020.01089.
155. Vermorken AJ, Zhu J, Andres E. Obesity and colorectal cancer risk: the role of oxidative stress. Gut. 2014;63:529–30. https://doi.org/10.1136/gutjnl-2013-305561.
156. McDowell SAC, Luo RBE, Arabzadeh A, Dore S, Bennett NC, Breton V, Karimi E, Rezanejad M, Yang RR, Lach KD, et al. Neutrophil oxidative stress mediates obesity-associated vascular dysfunction and metastatic transmigration. Nat Cancer. 2021;2:545–62. https://doi.org/10.1038/s43018-021-00194-9.
157. Leanza G, Conte C, Cannata F, Isgro C, Piccoli A, Strollo R, Quattrocchi CC, Papalia R, Denaro V, Maccarrone M, et al. Oxidative stress in postmenopausal women with or without obesity. Cells. 2023;12. https://doi.org/10.3390/cells12081137.
158. Dorjgochoo T, Gao YT, Chow WH, Shu XO, Yang G, Cai Q, Rothman N, Cai H, Li H, Deng X, et al. Obesity, age, and oxidative stress in middle-aged and older women. Antioxid Redox Signal. 2011;14:2453–60. https://doi.org/10.1089/ars.2010.3337.
159. Ahn B, Pharaoh G, Premkumar P, Huseman K, Ranjit R, Kinter M, Szweda L, Kiss T, Fulop G, Tarantini S, et al. Nrf2 deficiency exacerbates age-related contractile dysfunction and loss of skeletal muscle mass. Redox Biol. 2018;17:47–58. https://doi.org/10.1016/j.redox.2018.04.004.
160. Balasubramanian P, Kiss T, Gulej R, Nyul Toth A, Tarantini S, Yabluchanskiy A, Ungvari Z, Csiszar A. Accelerated aging induced by an unhealthy high-fat diet: initial evidence for the role of Nrf2 deficiency and impaired stress resilience in cellular senescence. Nutrients. 2024;16. https://doi.org/10.3390/nu16070952.
161. Bautista-Nino PK, Portilla-Fernandez E, Vaughan DE, Danser AH, Roks AJ. DNA damage: a main determinant of vascular aging. Int J Mol Sci. 2016;17. https://doi.org/10.3390/ijms17050748.
162. Bose C, Alves I, Singh P, Palade PT, Carvalho E, Borsheim E, Jun SR, Cheema A, Boerma M, Awasthi S, Singh SP. Sulforaphane prevents age-associated cardiac and muscular dysfunction through Nrf2 signaling. Aging Cell. 2020;19:e13261. https://doi.org/10.1111/acel.13261.
163. Fulop GA, Kiss T, Tarantini S, Balasubramanian P, Yabluchanskiy A, Farkas E, Bari F, Ungvari Z, Csiszar A. Nrf2 deficiency in aged mice exacerbates cellular senescence promoting cerebrovascular inflammation. Geroscience. 2018;40:513–21. https://doi.org/10.1007/s11357-018-0047-6.
164. Kubben N, Zhang W, Wang L, Voss TC, Yang J, Qu J, Liu GH, Misteli T. Repression of the antioxidant NRF2 pathway in premature aging. Cell. 2016;165:1361–74. https://doi.org/10.1016/j.cell.2016.05.017.
165. Martin-Montalvo A, Villalba JM, Navas P, de Cabo R. NRF2, cancer and calorie restriction. Oncogene. 2011;30:505–20. https://doi.org/10.1038/onc.2010.492.
166. Pearson KJ, Lewis KN, Price NL, Chang JW, Perez E, Cascajo MV, Tamashiro KL, Poosala S, Csiszar A, Ungvari Z, et al. Nrf2 mediates cancer protection but not prolongevity induced by caloric restriction. Proc Natl Acad Sci U S A. 2008;105:2325–30.
167. Ungvari Z, Bailey-Downs L, Sosnowska D, Gautam T, Koncz P, Losonczy G, Ballabh P, de Cabo R, Sonntag WE, Csiszar A. Vascular oxidative stress in aging: a homeostatic failure due to dysregulation of Nrf2-mediated antioxidant response. Am J Physiol Heart Circ Physiol. 2011;301:H363-372.
168. Ungvari Z, Tarantini S, Nyul-Toth A, Kiss T, Yabluchanskiy A, Csipo T, Balasubramanian P, Lipecz A, Benyo Z, Csiszar A. Nrf2 dysfunction and impaired cellular resilience to oxidative stressors in the aged vasculature: from increased cellular senescence to the pathogenesis of age-related vascular diseases. Geroscience. 2019;41:727–38. https://doi.org/10.1007/s11357-019-00107-w.
169. Collins AR, Lyon CJ, Xia X, Liu JZ, Tangirala RK, Yin F, Boyadjian R, Bikineyeva A, Pratico D, Harrison DG, Hsueh WA. Age-accelerated atherosclerosis correlates with failure to upregulate antioxidant genes. Circ Res. 2009;104:e42-54. https://doi.org/10.1161/CIRCRESAHA.108.188771.
170. Morrison CD, Pistell PJ, Ingram DK, Johnson WD, Liu Y, Fernandez-Kim SO, White CL, Purpera MN, Uranga RM, Bruce-Keller AJ, Keller JN. High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: implications for decreased Nrf2 signaling. J Neurochem. 2010;114:1581–9. https://doi.org/10.1111/j.1471-4159.2010.06865.x.
171. Tanaka Y, Aleksunes LM, Yeager RL, Gyamfi MA, Esterly N, Guo GL, Klaassen CD. NF-E2-related factor 2 inhibits lipid accumulation and oxidative stress in mice fed a high-fat diet. J Pharmacol Exp Ther. 2008;325:655–64.
172. Ungvari ZI, Bailey-Downs L, Gautam T, Jimenez R, Losonczy G, Zhang C, Ballabh P, Recchia FA, Wilkerson

DC, Sonntag WE, et al. Adaptive induction of NF-E2-Related Factor-2-driven antioxidant genes in endothelial cells in response to hyperglycemia. Am J Physiol Heart Circ Physiol. 2011;300:H1133-1140. https://doi.org/10.1152/ajpheart.00402.2010.
173. Ungvari Z, Bagi Z, Feher A, Recchia FA, Sonntag WE, Pearson K, de Cabo R, Csiszar A. Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2. Am J Physiol Heart Circ Physiol. 2010;299:H18-24.
174. Feletto E, Kohar A, Mizrahi D, Grogan P, Steinberg J, Hughes C, Watson WL, Canfell K, Yu XQ. An ecological study of obesity-related cancer incidence trends in Australia from 1983 to 2017. Lancet Reg Health West Pac. 2022;29:100575. https://doi.org/10.1016/j.lanwpc.2022.100575.
175. Li H, Boakye D, Chen X, Hoffmeister M, Brenner H. Association of body mass index with risk of early-onset colorectal cancer: systematic review and meta-analysis. Official journal of the American College of Gastroenterology| ACG. 2021;116:2173-2183.
176. Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y, Qin H. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PloS one. 2013;8:e53916.
177. Lei X, Song S, Li X, Geng C, Wang C. Excessive body fat at a young age increases the risk of colorectal cancer: a systematic review and meta-analysis. Nutrition and Cancer. 2021;73:1601–12.
178. Shen X, Wang Y, Zhao R, Wan Q, Wu Y, Zhao L, Wu X. Metabolic syndrome and the risk of colorectal cancer: a systematic review and meta-analysis. Int J Colorectal Dis. 2021;36:2215–25.
179. Mandic M, Li H, Safizadeh F, Niedermaier T, Hoffmeister M, Brenner H. Is the association of overweight and obesity with colorectal cancer underestimated? An umbrella review of systematic reviews and meta-analyses (Vol 38, pg 135, 2023). Eur J Epidemiol. 2024.
180. Mandic M, Safizadeh F, Niedermaier T, Hoffmeister M, Brenner H. Association of overweight, obesity, and recent weight loss with colorectal cancer risk. JAMA network Open. 2023;6:e239556–e239556.
181. Shi X, Deng G, Wen H, Lin A, Wang H, Zhu L, Mou W, Liu Z, Li X, Zhang J. Role of body mass index and weight change in the risk of cancer: a systematic review and meta-analysis of 66 cohort studies. J Glob Health. 2024;14. https://doi.org/10.7189/jogh.14.04067.
182. Zhang C, Cheng Y, Luo D, Wang J, Liu J, Luo Y, Zhou W, Zhuo Z, Guo K, Zeng R. Association between cardiovascular risk factors and colorectal cancer: a systematic review and meta-analysis of prospective cohort studies. EClinical Medicine. 2021;34. https://doi.org/10.1016/j.eclinm.2021.100794.
183. Shi Q, Wang Y, Hao Q, Vandvik PO, Guyatt G, Li J, Chen Z, Xu S, Shen Y, Ge L, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. Lancet. 2024;403:e21–31. https://doi.org/10.1016/S0140-6736(24)00351-9.
184. Ansari S, Khoo B, Tan T. Targeting the incretin system in obesity and type 2 diabetes mellitus. Nat Rev Endocrinol. 2024. https://doi.org/10.1038/s41574-024-00979-9.
185. Aslam B, Bin Zafar MD, Changez MIK, Abdullah M, Safwan M, Qamar B, Shinwari A, Rai S. Exploring the potential impact of GLP-1 receptor agonists in cancer therapy. Minerva Endocrinol (Torino). 2023. https://doi.org/10.23736/S2724-6507.23.04101-5.
186. Chierici A, Amoretti P, Drai C, De Fatico S, Barriere J, Schiavo L, Iannelli A. Does bariatric surgery reduce the risk of colorectal cancer in individuals with morbid obesity? A Systematic Review and Meta-Analysis. Nutrients. 2023;15. https://doi.org/10.3390/nu15020467.
187. Davey MG, Ryan OK, Ryan EJ, Donlon NE, Reynolds IS, Fearon NM, Martin ST, Heneghan HM. The impact of bariatric surgery on the incidence of colorectal cancer in patients with obesity-a systematic review and meta-analysis of registry data. Obes Surg. 2023;33:2293–302. https://doi.org/10.1007/s11695-023-06674-4.
188. Bailly L, Fabre R, Pradier C, Iannelli A. Colorectal cancer risk following bariatric surgery in a nationwide study of French individuals with obesity. JAMA Surg. 2020;155:395–402. https://doi.org/10.1001/jamasurg.2020.0089.
189. Xiang L, Xiao Y, Xu Z, Luo H, Ren X, Wei Q, Zhu Z, Jiang Y, Tang Y, He H, et al. Association of diabetes risk reduction diet with renal cancer risk in 101,755 participants: a prospective study. J Transl Med. 2023;21:684. https://doi.org/10.1186/s12967-023-04555-z.
190. Wang L, Du M, Wang K, Khandpur N, Rossato SL, Drouin-Chartier JP, Steele EM, Giovannucci E, Song M, Zhang FF. Association of ultra-processed food consumption with colorectal cancer risk among men and women: results from three prospective US cohort studies. BMJ. 2022;378:e068921. https://doi.org/10.1136/bmj-2021-068921.
191. Pan B, Lai H, Ma N, Li D, Deng X, Wang X, Zhang Q, Yang Q, Wang Q, Zhu H, et al. Association of soft drinks and 100% fruit juice consumption with risk of cancer: a systematic review and dose-response meta-analysis of prospective cohort studies. Int J Behav Nutr Phys Act. 2023;20:58. https://doi.org/10.1186/s12966-023-01459-5.
192. Jatho A, Myung SK, Kim J, Han SS, Kim SY, Ju W. Consumption of sugar-sweetened soft drinks and risk of gastrointestinal cancer: a systematic review and meta-analysis of observational studies. Oncology. 2024;102:141–56. https://doi.org/10.1159/000531110.
193. Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S, Meyerhardt JA, Chan AT, Willett WC, Wu K, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. Gut. 2021;70:2330–6. https://doi.org/10.1136/gutjnl-2020-323450.
194. Feng L, Gao J, Xia W, Li Y, Lowe S, Yau V, Ma S, Zhou Z, Ding P, Cheng C, et al. Association of sugar-sweetened beverages with the risk of colorectal cancer: a systematic review and meta-analysis. Eur J Clin Nutr. 2023;77:941–52. https://doi.org/10.1038/s41430-023-01302-x.

195. Chazelas E, Srour B, Desmetz E, Kesse-Guyot E, Julia C, Deschamps V, Druesne-Pecollo N, Galan P, Hercberg S, Latino-Martel P, et al. Sugary drink consumption and risk of cancer: results from NutriNet-Sante prospective cohort. BMJ. 2019;366:l2408. https://doi.org/10.1136/bmj.l2408.
196. Ruff RR, Zhen C. Estimating the effects of a calorie-based sugar-sweetened beverage tax on weight and obesity in New York City adults using dynamic loss models. Ann Epidemiol. 2015;25:350–7. https://doi.org/10.1016/j.annepidem.2014.12.008.
197. Phonsuk P, Vongmongkol V, Ponguttha S, Suphanchaimat R, Rojroongwasinkul N, Swinburn BA. Impacts of a sugar sweetened beverage tax on body mass index and obesity in Thailand: A modelling study. PLoS One. 2021;16:e0250841. https://doi.org/10.1371/journal.pone.0250841.
198. Lin BH, Smith TA, Lee JY, Hall KD. Measuring weight outcomes for obesity intervention strategies: the case of a sugar-sweetened beverage tax. Econ Hum Biol. 2011;9:329–41. https://doi.org/10.1016/j.ehb.2011.08.007.
199. Lee MM, Barrett JL, Kenney EL, Gouck J, Whetstone LM, McCulloch SM, Cradock AL, Long MW, Ward ZJ, Rohrer B, et al. A sugar-sweetened beverage excise tax in California: projected benefits for population obesity and health equity. Am J Prev Med. 2024;66:94–103. https://doi.org/10.1016/j.amepre.2023.08.004.
200. Durand CP, Andalib M, Dunton GF, Wolch J, Pentz MA. A systematic review of built environment factors related to physical activity and obesity risk: implications for smart growth urban planning. Obes Rev. 2011;12:e173-182. https://doi.org/10.1111/j.1467-789X.2010.00826.x.
201. Bezzina A, Clarke ED, Ashton L, Watson T, James CL. Workplace health promotion programs targeting smoking, nutrition, physical activity, and obesity in men: a systematic review and meta-analysis of randomized controlled trials. Health Educ Behav. 2024;51:113–27. https://doi.org/10.1177/10901981231208396.
202. Ungvari Z, Fekete M, Fekete JT, Grosso G, Ungvari A, Gyorffy B. Adherence to the Mediterranean diet and its protective effects against colorectal cancer: a meta-analysis of 26 studies with 2,217,404 participants. Geroscience. 2024. https://doi.org/10.1007/s11357-024-01296-9.
203. Intzandt B, Sanami S, Huck J, group P-AR, Villeneuve S, Bherer L, Gauthier CJ. Sex-specific relationships between obesity, physical activity, and gray and white matter volume in cognitively unimpaired older adults. Geroscience. 2023;45:1869-1888. https://doi.org/10.1007/s11357-023-00734-4.
204. Loosen SH, Roderburg C, Jordens MS, Fluegen G, Luedde T, Kostev K. Overweight and obesity determine the risk for gastrointestinal cancer in a sex-dependent manner: a retrospective cohort study of 287,357 outpatients in Germany. Cancers (Basel). 2022;14. https://doi.org/10.3390/cancers14040931.
205. Mandic M, Safizadeh F, Niedermaier T, Hoffmeister M, Brenner H. Association of overweight, obesity, and recent weight loss with colorectal cancer risk. JAMA Netw Open. 2023;6:e239556. https://doi.org/10.1001/jamanetworkopen.2023.9556.
206. Quarleri J, Delpino MV. The interplay of aging, adipose tissue, and COVID-19: a potent alliance with implications for health. Geroscience. 2024;46:2915–32. https://doi.org/10.1007/s11357-023-01058-z.
207. Ler P, Ploner A, Finkel D, Reynolds CA, Zhan Y, Jylhava J, Dahl Aslan AK, Karlsson IK. Interplay of body mass index and metabolic syndrome: association with physiological age from midlife to late-life. Geroscience. 2024;46:2605–17. https://doi.org/10.1007/s11357-023-01032-9.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.