

Risk of colorectal cancer after weight loss in the obese: a pooled cohort study

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Abstract

Background Though the link between obesity and colorectal cancer (CRC) is convincing, the impact of weight loss after obesity on CRC risk is unknown.

Methods This pooled study from the Multiethnic Cohort, Nurses' Health Study and Health Professionals Follow-Up Study included adults aged 45-75, with 3+ available body mass index (BMI) measures. The primary analysis included persons of all weights, with exposure (BMI) subjected to group-based trajectory modeling. Time-to-incident CRC was evaluated using accelerated failure time models. A subanalysis evaluated the risk of CRC in persons with obesity who had weight loss, compared to persons with stable obesity.

Results A total of 193,046 persons were analyzed (median age 49 years, 66% female). Among persons with severe degrees of obesity who lost weight, there was a longer CRC-free duration in whites (acceleration factor [AF] 2.30, 95% confidence interval [CI] 1.23-4.29; $P=0.01$), persons of "Other" race (AF 2.54, 95%CI 2.45-2.63; $P<0.001$), Asian/Native Hawaiian/Other Pacific Islanders (AF 1.11, 95%CI 1.06-1.18; $P<0.001$), and Black/African Americans (AF 1.09, 95%CI 1.07-1.10; $P<0.001$). BMI was not associated with altered CRC risk in Hispanic/Latinos. Among 40,606 persons with obesity who had weight loss, higher degrees of weight loss were associated with a longer CRC-free duration. While weight loss of 5-10% had an AF of 1.14 (95%CI 1.04-1.24; $P=0.01$), the optimal degree of weight loss was 15-20%, AF 1.53 (95%CI 1.28-1.83; $P<0.001$).

Conclusions Weight loss after obesity is associated with a lower CRC risk in diverse populations. In persons with obesity, 15-20% weight loss appears to be optimal.

Keywords Colorectal cancer, group-based trajectory modeling, obesity, weight loss

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Introduction

The evidence that obesity is a risk factor for future colorectal adenocarcinoma (CRC) is overwhelming, and of critical public health importance. However, the impact of weight loss on CRC risk mitigation in obese persons is unknown, and has been highlighted by the National Cancer Institute (NCI) as a focus area for future research [1,2]. Population-based studies have found inconsistent results regarding the association between weight loss and future CRC development [1,2]. Even in cohorts undergoing intentional weight loss via bariatric surgery, the impact on future CRC risk is unknown. Indeed, some studies suggest weight loss may be associated with a lower risk of future CRC [3-8], whereas others demonstrated a higher risk [9-11]. Thus, while it would stand to reason that

mitigating obesity would decrease future CRC risk, this is not supported by current evidence.

Part of the difficulty in disentangling the controversy is that prior studies are limited. First, studies evaluating persons undergoing bariatric surgery limit generalizability: bariatric surgery is only indicated for severe forms of obesity, and while 42.4% of Americans are considered obese (body mass index [BMI] >30 kg/m²), only 9.2% are severely obese, qualifying for bariatric surgery based on BMI alone [5,6,9,12]. Second, prior studies lacked racially and ethnically diverse populations—a crucial point, as there are differences in the risks of obesity and CRC, and in access to weight-loss therapies, across different racial/ethnic groups. Third, previous analyses did not use large, granular data sources and thus had limited power. The methodologies of prior studies also pose limitations from the use of one-time obesity or administrative coding of obesity. We investigated the association between weight trajectories and time to CRC diagnosis in a pooled cohort, using 3 large longitudinal prospective cohorts to capture racially and ethnically diverse populations, and advanced methods to model changes in BMI over time. We further identified, among persons with obesity, whether and how much weight loss resulted in meaningful CRC risk reduction.

Materials and methods

In this analysis of existing data, we pooled data from 3 prospective cohorts: the Nurses' Health Study (NHS), the Health Professionals Follow-Up Study (HPFS), and the Multiethnic Cohort Study (MEC). We identified participants' weight and BMI, in order to create trajectories for BMI using group-based trajectory modeling (GBTM), and we performed multivariable modeling to determine the association between BMI trajectory and time to CRC diagnosis (incidence). We then conducted a dedicated subanalysis, limited to adults with obesity who underwent stable weight or weight loss, to identify the risk of CRC in persons with obesity who underwent weight loss. The purpose of this study structure was to first evaluate trends across all weights, evaluating differences across racial/ethnic groups, and then identify whether and how much weight

loss was necessary to alter CRC risk. This study was approved by the University of Miami Institutional Review Board and permission was granted from the cohorts.

Cohorts, study population, and pooling

All 3 cohorts (NHS, HPFS, MEC) are NCI-funded prospective cohort studies, well-established in the scientific literature. These cohorts evaluate baseline factors and follow individuals over time to collect longitudinal data at multiple time points via questionnaires, including weight, BMI, smoking status, and adjudicated outcomes (e.g., cancer diagnosis). The NHS and HPFS have evaluated females and males, respectively, since the 1970s [13]. The MEC was established in 1993 and includes >215,000 individuals living in Hawaii and California, of 5 main ethnicities: Japanese-, African-, and white-Americans, Native Hawaiians, and Hispanic/Latinos [14,15].

We included individuals aged 45–75, evaluating data from between January 1, 1993, and January 1, 2019, with at least 3 available BMIs to ensure adequate engagement and follow up. The BMI was self-reported from separate questionnaires, which were separated by at least 1 year. We excluded people with a history of cancer (apart from non-melanoma skin cancers) prior to inclusion in the cohort, as well as those who developed other cancers during follow-up, as this may have impacted BMI.

To ensure diversity of race, ethnicity and sex, cohorts were pooled. Pooling entailed harmonizing data across 3 cohorts, involving: 1) preliminary exploration; 2) categorization of variables by consistency; 3) harmonization according to consistency; 4) creation of a data dictionary; 5) concatenation into a single dataset; and 6) quality control. As the race/ethnicity self-report options differed for the NHS and HPFS, as compared to MEC, we categorized individuals as one of the following: White, Black or African American, Asian/Native Hawaiian/Other Pacific Islander ("AANHPI"), Hispanic or Latino, or Other.

The NHS and HPFS had options for race and ethnicity (Hispanic/Latino: yes/no) separately, but the MEC only offered ethnicity, not race (MEC categories: African American, Hawaiian, Hispanic or Latino, Japanese, or White). We therefore categorized an individual as "Hispanic or Latino" if they self-selected Hispanic or Latino in the MEC, but this category did not include persons in the NHS and HPFS, as it was impossible to disentangle their race and ethnicity (e.g., an individual could select White and Hispanic). Therefore, the Hispanic/Latino group only included persons from the MEC.

Outcome and exposures

The primary outcome was time to incident CRC, and primary exposure was BMI. Outcomes included CRC (colon, rectal, or overlapping cancers), which are adjudicated within these NCI-funded cohorts. To ensure we did not capture any BMIs that were related to a prevalent cancer (e.g., cancer-associated weight loss), any BMI data within 1 year of the end of follow up were excluded [16,17]. BMI data were subjected to group-

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based modeling techniques. In GBTM, patterns of changes over time are identified, and individuals are assigned to a category (or “class”). In creating these trajectories, we accounted for the year of weight (to consider differing trends over time) and age. As this allows for longitudinal patterns (BMI over many years), it is more informative than cross-sectional evaluation of BMI alone. In the GBTM, we chose the number of classes using the Bayesian information criterion (BIC). Goodness-of-fit was ensured by a mean posterior probability of each class >75%, as well as maximum log-likelihood and likelihood ratio tests. In addition to age, covariates included sex and factors associated with CRC: diabetes, smoking, and family history of CRC, which were all self-reported in the questionnaires.

Statistical analysis

Given the large sample size, we created different models for each race/ethnicity, which we had specified *a priori*, and a separate regression model was then constructed for each race/ethnicity. Descriptive statistics were obtained, and characteristics of those who did and did not develop CRC were compared. We found that <1% of data were missing, so imputation was not performed. For GBTM, and to identify distinct BMI trajectories over ages, a latent class mixed model with a random intercept was fitted. The outcome BMI values were log-transformed for better adherence to the model assumptions, and a 2-quantile spline was utilized for link function approximation. The modeling employed the “*lcm*” package in R, starting with a single latent class to establish baseline trajectories [18,19]. We selected the number of classes using the BIC local extremum and clinical input. We then conducted multivariable analyses for each race/ethnic group, using a time-to-event model. As the proportional hazard assumption was not met for white and AANHPI racial/ethnic groups and models did not converge for Blacks and other racial/ethnic groups, we opted for accelerated failure time models for all race/ethnicities. Model adjustments were made for sex, smoking status, family history, diabetes and age, while accounting for within-cohort correlation through clustering by cohort—except for Latinos, who were all from the MEC cohort. Acceleration factors (AFs) were estimated for trajectory class membership and covariate. AF >1 suggests that the CRC is expected to occur later, that is, cancer-free time is increased. AF <1 suggests that CRC is expected to occur sooner, and cancer-free time is reduced. Robust sandwich estimators were used and model coefficient estimates, along with 95% confidence intervals and P-values, were determined. Finally, cumulative hazard plots were created to display the estimated cumulative hazard for cancer occurrence over time for each class, visualizing differences in the risk profiles across the racial/ethnic groups. *A priori* sample size calculations were performed. For GBTM, models obtain accurate estimates of slope at a sample size of 500, which our pooled cohort amply satisfied [20]. We estimated <3% lifetime incidence of CRC [21], and preliminary sample size showed a pooled cohort of >60,000 individuals [21]. We expected >99% power at a 0.05 significance level to detect a hazard ratio of 0.2 [22].

Subanalysis

A dedicated subanalysis was conducted to identify the association between weight loss after obesity and CRC. We included individuals from the pooled cohort with obesity: a BMI ≥ 30 kg/m² for non-AANHPIs and ≥ 27.5 kg/m² for persons who were AANHPI (as defined by the World Health Organization) [23-25], who had stable weight or weight loss (between first and last time point).

We classified weight loss categorically between first and last time point, to optimize clinical applicability. There is no standardized definition of weight loss, though >5% weight loss is thought to have beneficial, clinically meaningful effects [21,26-29]. We classified weight loss increments to be >5% to $\leq 10\%$, >10% to $\leq 15\%$, >15% to $\leq 20\%$, and >20%. Persons with stable weight after obesity ($\pm 5\%$) were used as a reference. We chose a categorical approach to be clinically applicable (e.g., clinicians often tout a 5-10% weight-loss goal to reverse liver steatosis) [30]. Like the primary analysis, the primary outcome in the subanalysis was time to incident CRC. Here, the primary exposure was weight loss, treated categorically, and adjustment included the same covariates as the primary analysis. Here too, the proportional hazards assumption was not met so accelerated failure time models were used for analyses. Finally, we conducted a sensitivity analysis, where we averaged the percent change in BMI at each time point (compared to initial). By doing so, we were able to assess the relative change in BMI over time, highlighting the overall trend, versus large differences between early and later BMIs.

Data analysis and ethical approvals

Data were analyzed on the Channing Division of Network Medicine's IT infrastructure at Brigham and Women's Hospital, in conjunction with NHS/HPFS requirements. Analyses were performed using R version 4.2.0. Reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies (Supplementary Table 1).

Results

We identified 193,046 persons who met the inclusion criteria and were included in our pooled cohort: the median age at cohort entry was 49 years, and 127,214 (65.9%) were female. CRC developed in 4104 (2.12%) individuals, a median of 21 years after cohort entry.

Those who developed CRC were more likely to be White (77.58% vs. 66.92%, $P < 0.001$), and more likely to report a family history of CRC (11.92% vs. 9.19%, $P < 0.001$; Table 1). Those who did not develop CRC were more likely to have never smoked (46.77% vs. 42.81%, $P < 0.001$). Those who developed CRC were less likely to be underweight or normal weight at cohort entry ($P = 0.03$), and gained more weight during follow up (BMI increase 3.44% vs. 2.22%, $P < 0.001$).

For each racial/ethnic group, we performed GBTM, and participants were grouped into 5 BMI trajectory classes, as shown in Fig. 1. We selected BMI trajectory classes as references that began in normal to overweight ranges and gained the smallest amount of weight. The created trajectories were then included in the multivariable models, which, as noted above, were conducted separately for each race/ethnicity (Table 2). We found that among persons in this class, there was longer CRC-free duration in Whites (AF 2.30, 95%CI 1.23-4.29; $P=0.01$), AANHPIs (AF 1.11, 95%CI 1.06-1.18; $P<0.001$), Black/African American (AF 1.09, 95%CI 1.07-1.10; $P<0.001$), and Others (AF 2.54, 95%CI 2.45-2.63; $P<0.001$). This suggests a protective effect of weight loss after severe obesity. However, it was not statistically significantly associated with time to CRC in Hispanic/Latinos.

In addition, findings regarding BMI class differed by racial/ethnic group. In Whites, compared to normal weight persons who gained weight over time, persons who were overweight but lost weight had a longer CRC-free duration (AF 1.94, 95%CI 1.16-3.23; $P=0.01$). For Black/African Americans who were obese and lost weight, the protective effect was smaller (AF 1.18, 95%CI 1.09-1.28; $P<0.001$). Notably, for Black/African Americans who went from underweight to obese,

the AF was 8.42 (95%CI 2.10-33.71; $P=0.003$). However, this was because only 2 persons in the class developed CRC, while a sensitivity analysis using 4 classes showed a non-significant association for Black/African Americans (AF 1.01, 95%CI 0.83-1.22; $P=0.95$). Among persons of Other race/ethnicity, those starting with BMI <20 kg/m² but gaining weight (endpoint BMI >30 kg/m²) had a shorter CRC-free duration (AF 0.55, 95%CI 0.54-0.55; $P<0.001$). Otherwise, moderate weight gain (BMI <25 kg/m² to BMI >25 kg/m²) and moderate weight loss (BMI <30 kg/m² to BMI <25 kg/m²) were both associated with a longer CRC-free duration. Among the Hispanic/Latino group, there was no significant finding among any BMI class.

Across racial/ethnic groups, current smoking was associated with earlier CRC, most pronounced in Whites (AF 0.85, 95%CI 0.81-0.89; $P<0.001$) and AANHPIs (AF 0.90, 95%CI 0.83-0.98; $P=0.02$). Similarly, a family history of CRC was associated with earlier CRC, as seen most strongly in Whites (AF 0.84, 95%CI 0.78-0.90; $P<0.001$). Over and above other explanatory variables, diabetes was non-significantly associated with earlier CRC diagnosis, whereas female sex was non-significantly associated with a longer CRC-free duration.

Table 1 Pooled cohort characteristics, by those who did and did not develop CRC (n = 19,3046)

Characteristics	Developed CRC (n=4104)	Did not develop CRC (n=188,942)	P-value
Age at cohort entry, median (IQR)	51.00 (44.00-58.00)	49.00 (42.00-57.00)	<0.001
Female sex	2706 (65.94%)	124508 (65.90%)	0.97
Race			<0.001
White	3184 (77.58%)	126435 (66.92%)	
Black/African American	148 (3.61%)	10335 (5.47%)	
AANHPI	457 (11.14%)	31237 (16.53%)	
Latino	168 (4.09%)	15305 (8.10%)	
Other	147 (3.58%)	5630 (2.98%)	
BMI at entry, median (IQR)	24.45 (22.13-27.30)	24.30 (21.95-27.30)	0.01
BMI at cohort entry			0.03
Underweight	68 (1.66%)	3264 (1.73%)	
Normal weight	2149 (52.36%)	103565 (54.81%)	
Overweight	1393 (33.94%)	59444 (31.46%)	
Class 1 Obesity	367 (8.94%)	16790 (8.89%)	
Class 2 Obesity	96 (2.34%)	4284 (2.27%)	
Class 3 Obesity	31 (0.76%)	1595 (0.84%)	
Change in BMI during follow up, median (IQR)	1.67 (0.71-3.40)	2.10 (0.90-4.02)	<0.001
Percent change in BMI during total follow up, median (IQR)	3.44 (-2.21 to 11.90)	2.22 (-5.72 to 11.67)	<0.001
Type 2 diabetes	237 (5.77%)	10738 (5.68%)	0.002
Smoking			<0.001
Current	1015 (24.73%)	37419 (19.80%)	
Prior	1276 (31.09%)	60687 (32.12%)	
Never	1757 (42.81%)	88372 (46.77%)	
Unknown	56 (1.36%)	2464 (1.30%)	
Reported family history of CRC	489 (11.92%)	17362 (9.19%)	<0.001
Duration of follow up, years (median, IQR)	17.00 (12.00-24.00)	32.00 (17.00-38.00)	<0.001
Age at CRC diagnosis (years), median (IQR)	72.00 (79.00-65.00)	n/a	
Alive at end of follow up	1313 (31.99%)	118904 (62.93%)	<0.001

CRC, colorectal cancer; IQR, interquartile range; AANHPI, Asian/Native Hawaiian/Other Pacific Islander; BMI, body mass index

Table 2 Results of multivariable accelerated failure time models, by racial/ethnic group

Variables	White (n=129,619)	P-value	Black/ African American (n=10,483)	P-value	AANHPI (n=31,694)	P-value	Hispanic/ Latino (n=15,473)	P-value	Other (n=5777)	P-value
Age	0.96 (0.94-0.98)	<0.001	0.99 (0.98-0.99)	<0.001	0.99 (0.98-1.00)	0.01	0.99 (0.99-0.997)	<0.001	0.96 (0.95-0.96)	<0.001
Female sex	1.26 (0.95-1.67)	0.11	1.07 (0.94-1.22)	0.32	0.97 (0.91-1.04)	0.43	1.02 (1-1.05)	0.09	-	-
BMI Class, by GBTM										
Class 1	0.93 (0.75-1.17)	0.55	1.18 (1.09-1.28)	<0.001	0.98 (0.95-1.01)	0.17	0.96 (0.91-1.02)	0.16	0.55 (0.54-0.55)	<0.001
Class 2	2.30 (1.23-4.29)	0.01	1.09 (1.07-1.10)	<0.001	1.11 (1.06-1.18)	<0.001	1.06 (0.91-1.23)	0.45	2.54 (2.45-2.63)	<0.001
Class 3	1.94 (1.16-3.23)	0.01	0.97 (0.86-1.09)	0.64	Reference 1.01	0.15	1.03 (0.99-1.08)	0.11	1.91 (1.90-1.91)	<0.001
Class 4	Reference 1.05	-	Reference 8.42	-	(1.00-1.01) 0.96	0.09	1.03 (0.96-1.09)	0.45	Reference 1.16	-
Class 5	(0.98-1.13)	0.17	(2.10-33.71)	0.003	(0.92-1.01)		reference	-	(1.16-1.17)	<0.001
Diabetes	0.89 (0.78-1.02)	0.1	1.02 (0.92-1.12)	0.73	0.97 (0.95-0.99)	0.01	0.97 (0.93-1.00)	0.08	0.86 (0.65-1.14)	0.29
Smoking						0.02				
Current	0.85 (0.81-0.89)	<0.001	0.95 (0.85-1.06)	0.36	0.90 (0.83-0.98)	0.19	1.00 (0.96-1.05)	0.87	1.36 (1.36-1.37)	<0.001
Prior	0.95 (0.89-1.01)	0.1	1.02 (1.00-1.05)	0.048	0.97 (0.92-1.02)	<0.001	1.00 (0.97-1.03)	0.96	1.07 (1.05-1.09)	<0.001
FH of CRC	0.84 (0.78-0.90)	<0.001	0.88 (0.75-1.04)	0.13	0.98 (0.97-0.99)		1 (0.95-1.05)	0.98	1.15 (1.05-1.27)	0.004
AIC	15758.08		1337.896		5015.77		1663.1		664.06	
Loglik (model)	-7867***		-656.9***		-2495.9***		-819.5***		-321***	

* <0.05 ** <0.001 *** <0.001 for likelihood ratio test (LRT). Acceleration factors (AFs) and corresponding 95% CIs are provided in Table 2

+ We selected BMI trajectory classes as references that began normal to overweight ranges and gained the smallest amount of weight. Classes are not defined the same across racial/ethnic groups, as different models were run, but Class 2 represents persons who started with the highest levels of BMI and decreased over time

AANHPI, Asian/Native Hawaiian/Other Pacific Islander; BMI, body mass index; GBTM, group-based trajectory modeling; CI, confidence interval; AANHPI, Asian/Native Hawaiian/Other Pacific Islander; FH, family history; CRC, colorectal cancer; AIC, Akaike information criterion

Subanalysis, evaluating persons with obesity

We identified 40,606 persons with obesity, who had stable weight or weight loss (between first and last time point). Of these, 659 (1.62%) developed CRC. Those who developed CRC were more likely to be White (72.84% vs. 65.39%, $P<0.001$) and more likely to report having type 2 diabetes (13.05% vs. 10.37%, $P=0.01$). The 2 groups had similar starting BMIs at cohort entry: 31.06 kg/m² in those who developed CRC versus 31.00 kg/m² in those who did not. Those who developed CRC were less likely to have lost greater degrees of weight. For example, weight loss of $>20\%$ was less common in those developed CRC (6.22% vs. 13.94%, $P<0.001$).

Table 3 depicts the results of multivariable accelerated failure time models. Increasing age was associated with a shorter CRC-free duration (AF 0.97, 95%CI 0.97-0.98; $P<0.001$), as was reporting a history of diabetes (AF 0.84, 95%CI 0.75-0.95; $P=0.004$). More weight loss was associated with longer CRC-free duration. While weight loss of $>5\%$ but $\leq 10\%$ had an AF of 1.14 (95%CI 1.04-1.24; $P=0.01$), weight loss of $>10\%$ to

$\leq 15\%$ had AF 1.33 (95%CI 1.18-1.51; $P<0.001$). Even greater degrees of weight loss were associated with further extension of CRC-free duration. Weight loss of $>15\%$ to $\leq 20\%$ had AF 1.53 (95%CI 1.28-1.83; $P<0.001$), and $>20\%$ weight loss had AF 1.47 (95%CI 1.26-1.71; $P<0.001$). Race was not significantly associated with time to CRC.

Discussion

In one of the largest US population-based studies evaluating how longitudinal weight impacts CRC risk, we found that weight loss after obesity was associated with a longer CRC-free duration among persons of White, AANHPI, Black/African American and Other racial/ethnic groups, but this trend was not significant in Hispanic/Latino persons. We also found that in persons with obesity who lose weight (compared to those with stable obesity), weight loss reduces CRC risk, and that the optimal amount of weight loss is 15-20%. These data are

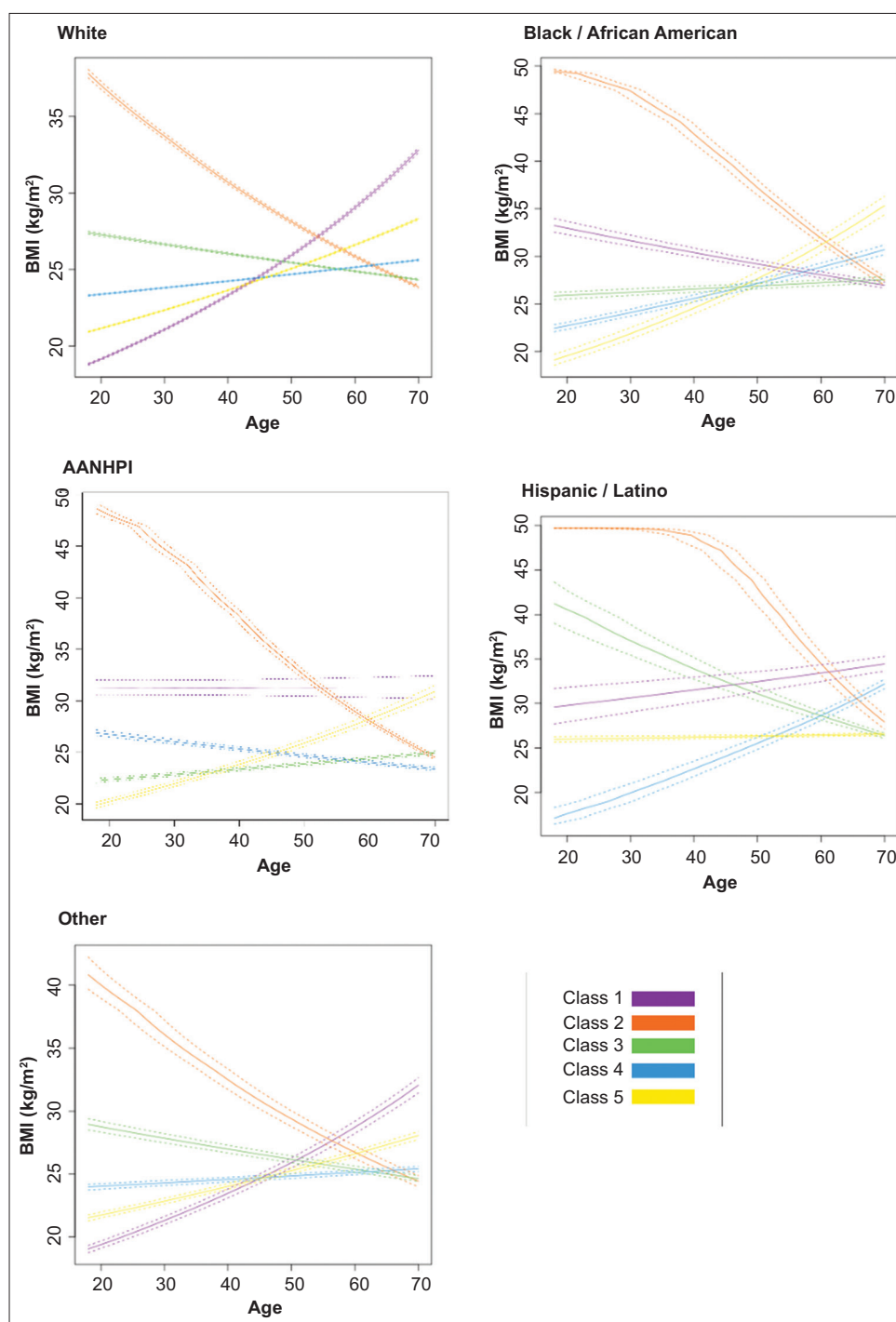


Figure 1 BMI trajectories of each racial/ethnic group, created using GBTM. Within the multivariable models, groups were further adjusted by age BMI, body mass index; GBTM, group-based trajectory modeling; AANHPI, Asian/Native Hawaiian/Other Pacific Islander

essential to understanding the public health impact of weight changes.

Among persons with obesity who underwent weight loss (compared to those who had stable weight), the degree of weight loss is important. While weight loss of >5% but ≤10% extends time to CRC incidence by 14%, higher degrees of

weight loss are more impactful: weight loss of >15% to ≤20% extends time to CRC incidence by 53%. Considering that CRC may take decades to develop, extending time to CRC by 53% is profound. These data can be used to guide clinicians and patients in determining how much weight loss is beneficial, and suggest that the typical 5-10% weight loss is important,

Table 3 Results of multivariable accelerated failure time models, among those persons with obesity who underwent weight loss

Variables	Acceleration factor time ratio (95%CI)	P-value
Age	0.97 (0.97-0.98)	<0.001
Female sex	0.94 (0.86-1.04)	0.23
Race		
White	(Reference)	
Black	1.07 (0.91-1.26)	0.42
AANHPI	0.98 (0.88-1.11)	0.73
Latino	1.04 (0.90-1.21)	0.59
Other	1.00 (0.78-1.26)	0.97
Weight loss		
±5%	(Reference)	
>5% to ≤10%	1.14 (1.04-1.24)	0.01
>10% to ≤15%	1.33 (1.18-1.51)	<0.001
>15% to ≤20%	1.53 (1.28-1.83)	<0.001
>20%	1.47 (1.26-1.71)	<0.001
Diabetes	0.84 (0.75-0.95)	0.004
Smoking		
Current	(Reference)	
Never	1.08 (0.95-1.22)	0.24
Past	1.05 (0.93-1.19)	0.40
FH of CRC	0.92 (0.82-1.04)	0.17
Cohort		
HPFS	(Reference)	
MEC	0.99 (0.84-1.15)	0.86
NHS	1.43 (1.00-2.05)	0.05
AIC	4139.23	
Loglik (model)	-2051.6*	

* <0.001 for likelihood ratio test (LRT)

CI, confidence interval; AANHPI, Asian/Native Hawaiian/Other Pacific Islander; FH, family history; CRC, colorectal cancer; AIC, Akaike information criterion

but higher degrees of weight loss should be considered, if deemed safe and feasible [31]. This also underlines the need to expand access to bariatric surgery; at present, only about 1% of those eligible receive surgical treatment for obesity, yet this represents an avenue to cancer risk mitigation [32,33]. Novel approaches, including endoscopic techniques and medical and pharmacologic approaches, should also be further utilized, particularly for those unable to undergo surgery [34,35].

As we describe above, prior studies have been limited. We overcame these limitations by pooling large and granular cohorts to ensure adequate sample size and diversity, evaluating persons with all classes of obesity, and using advanced methodologies and trajectories of change—in particular, using a dedicated subanalysis to investigate the amount of weight loss necessary to alter CRC risk. By doing so, we created one of the largest cohorts outside bariatric-specific patients in the US in which to evaluate pressing questions. While a recent study showed that weight loss reduces risk of obesity-related cancers, we were able to disaggregate CRC, one of the most common cancers within the US [36]. Our main finding, that mitigating severe degrees of obesity can reduce CRC risk, is particularly important in the age of expanding medical weight

loss therapies, and whether these should be used to alter CRC risk should be an area for future study.

Another important finding from our results is that, among all weights, BMI trajectory is not equally informative among different races and ethnicities. Trends were markedly different for different racial/ethnic groups, and this adds to the literature suggesting that BMI is imperfect [37,38]. In fact, for AANHPIs there are differing cutoffs for obesity classification by BMI, demonstrating the limitations of BMI in reflecting health [39,40]. Despite its ease of use, BMI does not capture metabolic health uniformly, and whether body composition, a more precise measure that includes visceral and subcutaneous fat, and lean mass, can be more informative should be investigated [41,42]. Furthermore, given that minorities have worse CRC-related outcomes (Black Americans have 20% higher CRC incidence and 40% higher CRC-specific mortality), our findings underline the need to identify drivers of CRC among racially and ethnically diverse populations [43,44]. It is important to note that for Hispanic/Latino persons, there was no significant association between BMI and CRC risk, suggesting that these findings need to be confirmed for this subgroup. Future studies should focus on under-investigated areas that may contribute to risk, including social, genetic and environmental factors. Finally, as we note above, if weight-loss therapies (medical, surgical, endoscopic) can reduce CRC risk among subgroups, access to these modalities should be studied to ensure it is equitable across groups.

There are limitations to this study. First, we were not able to determine the causality of weight changes, and determining the exact amount of intentional weight loss that is protective should be the focus of future studies. We were also unable to ascertain the modality of weight loss in our subanalysis. Second, the cohorts had some inherent selection bias. However, this remains the best avenue to investigate the questions of interest. Third, we used BMI and weight interchangeably, but BMI is imperfect and does not uniformly reflect health status. Fourth, there may have been unmeasured confounders, such as genetic predisposition to CRC, a limitation of all large cohort studies. Similarly, we are unable to account for detailed family history, CRC screenings, individual factors, and all comorbid medical conditions, including bariatric surgery. Fifth, we are also unable to establish causality between weight loss and CRC risk, given that this was an association study using pre-existing data. Sixth, there may have been misclassification of Hispanic/Latino persons, as we note in our Methods section, as harmonization across cohorts was unable to disentangle race and ethnicity. Seventh, we did not use a competing risk model, given that mortality was low in this cohort. Eighth, our analysis focused on long-term trajectories, to understand whether long-term changes in weight would impact CRC risk, but the analysis does not reflect whether short-term weight changes impact CRC risk, or whether time itself is a confounder. Ninth, within the available cohort data, we were unable to access specific data on CRC stage and treatment response, in order to understand stage- and treatment-specific impacts of obesity. Finally, while trajectories are the best available method to capture BMI changes across many years, fluctuations may or may not be captured depending on the timing of questionnaires. We

attempted to account for this in our subanalysis, where we used average percentage change to model BMI over time.

The strengths of our study are primarily related to the unique nature of the cohorts, with longitudinal data, robust statistical power after pooling (including sufficient power for a dedicated subanalysis of persons with obesity), the diversity of cohorts (racial/ethnic and geographic), and the use of advanced modeling methods. By conducting one of the largest US-focused population-based studies investigating the association between BMI trajectories and CRC risk, we contribute to the literature in a meaningful way. We found that BMI trajectories are not equally informative across racial/ethnic groups, underlining the need to study diverse populations to identify drivers of CRC risk. We also found that weight loss after obesity can reduce CRC risk, but that higher degrees of weight loss will see the most benefit. This answers an important public health question that supports ensuring access to weight-loss procedures, and further investigation of the potential benefits of the newer class of weight-loss medications to reduce CRC burden.

Summary Box

What is already known:

- There is a clear link between obesity and colorectal cancer (CRC)
- However, whether CRC risk is reduced after weight loss in persons with obesity is unknown
- The question of whether and how weight loss impacts CRC risk in persons with obesity has been difficult to answer, largely because of methodological limitations

What the new findings are:

- We overcame these limitations by utilizing a large, diverse pooled cohort and using advanced methodologies; doing so answers a timely question, given the obesity epidemic and recent increase in pharmacologic treatments for obesity
- In this analysis within a large, diverse pooled cohort, we found that weight loss after obesity does reduce CRC risk, and that the optimal loss is about 15-20%
- We found that body mass index trajectories are not equally informative across racial/ethnic groups, underlining the need to study diverse populations to identify drivers of CRC risk
- This answers an important public health question that supports ensuring access to weight-loss procedures, and further investigation of the potential benefits of the newer class of weight-loss medications to reduce the CRC burden

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Supplementary material

Supplementary Table 1 STROBE Statement—checklist of items that should be included in reports of observational studies

Items	Item No.	Recommendation	Line No.	Comments
Title & abstract				
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1-2	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	74-86	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	97-121	
Objectives	3	State specific objectives, including any prespecified hypotheses	117-121	
Methods				
Study design	4	Present key elements of study design early in the paper	126-136	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow up, and data collection	139-152	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	148-152;	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	n/a	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	171-184	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	139-146; 171-184	
Bias	9	Describe any efforts to address potential sources of bias	150-152	
Study size	10	Explain how the study size was arrived at	213-217	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	175-182	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	199-211	
		(b) Describe any methods used to examine subgroups and interactions	220-238	
		(c) Explain how missing data were addressed	191-192	
		(d) Cohort study—If applicable, explain how loss to follow up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	n/a	
		(e) Describe any sensitivity analyses	220-238	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow up, and analysed	249	
		(b) Give reasons for non-participation at each stage	n/a	
		(c) Consider use of a flow diagram	n/a	

(Contd...)

Supplementary Table 1 (*Continued*)

	Item No.	Recommendation	Line No.	Comments
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	Table 1	
		(b) Indicate number of participants with missing data for each variable of interest	n/a - 191-192	
		(c) Cohort study—Summarise follow-up time (e.g., average and total amount)	Table 1	
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	249-251	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a	
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2; 202-204	
		(b) Report category boundaries when continuous variables were categorized	Table 2	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a	
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	293-308; Table 3	
Discussion				
Key results	18	Summarise key results with reference to study objectives	312-318	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	362-383	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	385-398	
Generalisability	21	Discuss the generalisability (external validity) of the study results	385-390	
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	(title page)	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org