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Original Contribution

Body Mass Index at Different Adult Ages, Weight Change, and Colorectal Cancer Risk in the National Institutes of Health-AARP Cohort

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The authors investigated the relations of body mass index at different ages and adult weight change to incident colorectal cancer risk in the prospective National Institutes of Health–AARP Diet and Health Study (1995–1996), using a subcohort with repeated recall weights (273,679 participants; mean baseline age = 62.8 years). During 2,509,662 person-years follow-up, 4076 incident colorectal cancers were ascertained. For men, an increased risk of colon cancer but not rectal cancer was associated with body mass index at baseline age (per 5-kg/m^2 increase, hazard ratio (HR) = 1.18, 95% confidence interval (CI): 1.11, 1.25), at age 50 years (HR = 1.18, 95% CI: 1.10, 1.26), and at age 35 years (HR = 1.16, 95% CI: 1.07, 1.25) but less so at age 18 years. Weight gained between the ages of 18 and 35 years and between 18 years of age and the baseline age was associated with an increased risk of colon cancer in men (per 0.5-kg/year increase, HR = 1.18, 95% CI: 1.11, 1.25 and HR = 1.29, 95% CI: 1.16, 1.56, respectively). For women, relations throughout were weaker than those observed for men. These findings suggest that weight gains during early to middle adulthood have important influences on colon cancer risk, especially in men.

body mass index; colorectal cancer; weight gain

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; MHT, menopausal hormone therapy; NIH, National Institutes of Health.

Increased body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) is an established risk factor for colorectal cancer (CRC) (1). However, the influence of the timing and amount of adult weight change (loss and gain) on CRC risk is unclear.

In the absence of randomized trials of weight-change interventions and of large prospective cohort analyses of weight change throughout major life periods, observational studies have used recalled weight to estimate weight changes preceding cancer development. Weight gain through adulthood periods is associated with increased risks of postmenopausal breast (2–5) and endometrial (6–9) cancers, and weight loss or weight maintenance in early and middle adulthood is associated with a reduced risk of postmenopausal breast cancer (2–5, 10, 11). Data for CRC have been less consistent. For example, in some studies, investigators have evaluated the associations between body size changes at different age periods and colorectal neoplasm endpoints, including adenomas (12–15) and mortality (16), whereas in others, CRC risk was reported as part of other disease and cancer endpoints (17–21). However, no clear pattern of associations emerged. Studies in which incident CRC was the endpoint were limited to either men (22) or women (23, 24) only (so that hypothesized sex differences could not be tested (1)); combined colon and rectum together (25) (so that hypothesized subsite differences could not be tested (1)); or averaged weight change based on 2 age points only, typically ages 18 or 21 years and the cohort entry age (22, 23, 25).

In a previous report from the National Institutes of Health (NIH) and AARP Diet and Health Study, BMI was positively associated with colon cancer, more so in men

than in women (26). We now extend that knowledge by examining BMI at ages 18, 35, and 50 years and at the baseline age (mean = 63 years) in a subcohort using weight determinants at these ages and weight change during the 4 derived periods in relation to the risks colon and rectal cancer separately for men and women.

MATERIALS AND METHODS

Study population and case identification

The NIH-AARP Diet and Health Study was established in 1995 with a baseline questionnaire on medical history and lifestyle characteristics filled out by 566,401 AARP members aged 50–71 years who resided in 1 of 6 states or 2 metropolitan areas known to have high-quality cancer registries (27). A subcohort of 324,524 participants satisfactorily completed the baseline questionnaire and an additional risk factor questionnaire mailed in 1996, which included recalled weights at ages 18, 35, and 50 years. After exclusions (Web Appendix, available at http://aje.oxfordjournals.org/), this subcohort comprised 273,679 participants (168,294 men and 105,385 women) and formed the basis for this analysis.

NIH-AARP cohort members were followed annually (Web Appendix), and incident colon and rectal cancers were identified through the 8 state cancer registries using the *International Classification of Diseases for Oncology* codes. Subsites were categorized as proximal colon (cecum through transverse colon; codes 180 through 184), distal colon (splenic flexure through sigmoid colon; codes 185 through 187), and rectum (codes 199 and 209). Missing location data are noted as footnotes in Web Tables 5 and 6.

Exposure assessment

Height and weight were used to calculate BMI, which was divided into 9 categories (<18.5, 18.5–20.9 (reference), 21.0–22.9, 23.0–24.9, 25.0–27.4, 27.5–29.9, 30.0–32.4, 32.5–34.9, and ≥35.0). Baseline height was used to calculate BMI for each period.

Weight change was calculated as the difference in weight during 4 periods: from the ages of 18 to 35 years (to approximate change in early adulthood), from the ages of 35 to 50 years (to approximate change during middle adulthood and perimenopausal years in women), from age 50 years to the baseline age (to approximate change in late adulthood and postmenopausal years in women), and from age 18 years to

Table 1. Mean Body Mass Index Values and Weight Changes in Participants in the National Institutes of Health-AARP Diet and Health Study Cohort, 1995–1996

Sex and BMI[a] Category at Baseline	No. of Participants	Age, years	Mean[b] BMI[a] by Age				Mean[b] Weight Change by Age, kg			
			Baseline	18 years	35 years	50 years	18–35 years	35–50 years	50 years to Baseline	18 years to Baseline
Men										
<18.5	665	63.5	17.2	18.1	19.5	19.8	5.1	1.3	−8.7	−2.2
18.5–21.9	9,201	63.0	21.0	19.7	21.4	21.5	5.6	0.4	−1.7	4.3
22.0–22.9	9,588	62.9	22.6	20.3	22.3	2.8	6.5	1.4	−0.7	7.2
23.0–24.9	31,708	62.8	24.0	20.7	23.1	23.9	7.7	2.6	0.3	10.6
25.0–27.4	50,825	62.6	26.2	21.3	24.2	25.5	9.0	4.3	2.1	15.4
27.5–29.9	32,164	62.3	28.7	22.1	25.4	27.3	10.6	6.3	4.2	21.1
30.0–32.4	17,897	62.0	31.1	22.8	26.4	29.0	11.6	8.4	6.4	26.5
32.5–34.9	8,912	61.7	33.6	23.5	27.6	30.8	13.0	10.4	8.7	32.1
≥35	7,334	61.1	38.3	24.6	29.2	33.8	14.7	14.5	14.1	43.3
Women										
<18.5	1,263	62.6	17.5	19.2	19.2	19.0	−0.1	−0.5	−4.0	−4.6
18.5–21.9	18,092	61.8	20.7	19.9	20.4	20.8	1.4	1.1	−0.1	2.4
22.0–22.9	8,434	61.9	22.5	20.1	21.1	22.1	2.6	2.7	1.3	6.6
23.0–24.9	19,538	62.9	24.0	20.4	21.7	23.2	3.6	3.8	2.3	9.8
25.0–27.4	21,690	62.2	26.3	20.7	22.5	24.7	4.9	5.9	4.4	15.2
27.5–29.9	12,845	62.1	28.8	21.1	23.4	26.3	6.2	7.7	6.9	20.7
30.0–32.4	9,490	62.0	31.2	21.7	24.4	27.9	7.1	9.6	8.6	25.3
32.5–34.9	5,845	61.8	33.7	22.2	25.3	29.7	8.2	11.7	10.6	30.5
≥35	8,188	61.1	39.4	23.1	27.1	33.4	10.6	16.5	15.9	43.1

Abbreviation: BMI, body mass index.
[a] Weight (kg)/height (m)^2.
[b] Directly standardized to the age distribution of the cohort.

Table 2. Hazard Ratios for Incident Colon and Rectal Cancer in Relation to Body Mass Index Among Men in the National Institutes of Health-AARP Diet and Health Study Cohort, 1995–1996

	Colon Cancer[a]				Rectal Cancer[a]			
	No. of Cases	MVHR[b]	95% CI	*P* for Trend[c]	No. of Cases	MVHR[b]	95% CI	*P* for Trend[c]
BMI[d] at baseline				<0.0001				0.51
<18.5	6	0.89	0.39, 2.02		4	1.63	0.58, 4.59	
18.5–21.9	98	1.00	Referent		37	1.00	Referent	
22.0–22.9	93	0.91	0.68, 1.22		45	1.22	0.78, 1.91	
23.0–24.9	349	1.01	0.80, 1.27		150	1.20	0.82, 1.74	
25.0–27.4	600	1.07	0.86, 1.34		215	1.06	0.74, 1.53	
27.5–29.9	438	1.26	1.01, 1.58		149	1.15	0.79, 1.67	
30.0–32.4	249	1.29	1.01, 1.64		78	0.99	0.65, 1.49	
32.5–34.9	124	1.33	1.01, 1.75		44	1.22	0.77, 1.92	
≥35	113	1.53	1.16, 2.03		40	1.43	0.90, 2.28	
HR[c] per 5 kg/m^2		1.18	1.11, 1.25			1.03	0.93, 1.14	
BMI[d] at 50 years of age				<0.0001				0.25
<18.5	11	1.25	0.68, 2.31		4	1.16	0.42, 3.20	
18.5–21.9	142	1.00	Referent		58	1.00	Referent	
22.0–22.9	158	0.99	0.78, 1.25		58	0.90	0.62, 1.32	
23.0–24.9	414	0.91	0.75, 1.11		176	1.02	0.75, 1.38	
25.0–27.4	716	1.08	0.90, 1.30		249	0.94	0.70, 1.27	
27.5–29.9	315	1.14	0.93, 1.40		111	1.02	0.73, 1.41	
30.0–32.4	173	1.32	1.05, 1.66		62	1.15	0.79, 1.68	
32.5–34.9	92	1.62	1.24, 2.12		22	0.86	0.51, 1.44	
≥35	49	1.21	0.86, 1.70		22	1.41	0.85, 2.32	
HR[c] per 5 kg/m^2		1.18	1.10, 1.26			1.07	0.96, 1.19	
BMI[d] at 35 years of age				0.0001				0.15
<18.5	27	1.07	0.72, 1.58		10	0.99	0.52, 1.88	
18.5–21.9	389	1.00	Referent		158	1.00	Referent	
22.0–22.9	254	1.01	0.86, 1.19		87	0.89	0.68, 1.16	
23.0–24.9	512	1.00	0.88, 1.15		199	0.98	0.79, 1.22	
25.0–27.4	536	1.06	0.93, 1.21		183	0.91	0.73, 1.13	
27.5–29.9	214	1.32	1.12, 1.57		73	1.05	0.79, 1.41	
30.0–32.4	85	1.24	0.98, 1.58		29	1.08	0,72, 1.61	
≥32.5	53	1.44	1.07, 1.94		23	1.61	1.04, 2.51	
HR[c] per 5 kg/m^2		1.16	1.07, 1.25			1.10	0.97, 1.24	
BMI[d] at 18 years of age				0.06				0.91
<18.5	329	1.10	0.97, 1.25		118	1.03	0.83, 1.28	
18.5–21.9	916	1.00	Referent		352	1.00	Referent	
22.0–22.9	245	1.05	0.91, 1.21		94	1.02	0.81, 1.29	
23.0–24.9	316	1.10	0.97, 1.25		101	0.90	0.71, 1.12	
25.0–27.4	176	1.00	0.84, 1.18		68	1.00	0.77, 1.31	
27.5–29.9	48	1.13	0.84, 1.51		12	0.72	0.41, 1.28	
≥30.0	40	1.48	1.08, 2.03		17	1.51	0.91, 2.50	
HR[c] per 5 kg/m^2		1.10	1.00, 1.20			1.01	0.86, 1.18	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MVHR, multivariable hazard ratio.

[a] There were 28 men with synchronous colon and rectal cancers.

[b] Calculated using PROC PHREG in SAS, version 9.1. We took relative risk (used in the text) to be equivalent to HR. All analyses were adjusted for age (in the baseline hazard of the Cox regression) and the following covariates: race/ethnicity, educational level, physical activity level, smoking status, and alcohol consumption.

[c] Calculated after excluding subjects whose BMI at a given age was less than 18.5.

[d] Weight (kg)/height (m)^2.

Table 3. Hazard Ratios for Incident Colon and Rectal Cancer in Relation to Body Mass Index Women in the National Institutes of Health-AARP Diet and Health Study Cohort, 1995–1996

	Colon Cancer[a]				Rectal Cancer[a]			
	No. of Cases	MVHR[b]	95% CI	*P* for Trend[c]	No. of Cases	MVHR[b]	95% CI	*P* for Trend[c]
BMI[d] at baseline				0.20				0.45
<18.5	14	1.33	0.76, 2.30		6	1.94	0.82, 4.58	
18.5–21.9	148	1.00	Referent		43	1.00	Referent	
22.0–22.9	68	1.00	0.75, 1.34		22	1.15	0.68, 1.93	
23.0–24.9	176	1.08	0.87, 1.35		50	1.07	0.71, 1.63	
25.0–27.4	207	1.11	0.89, 1.38		64	1.21	0.82, 1.81	
27.5–29.9	127	1.15	0.90, 1.47		32	1.01	0.63, 1.61	
30.0–32.4	82	1.00	0.76, 1.32		20	0.85	0.49, 1.47	
32.5–34.9	54	1.07	0.78, 1.48		20	1.45	0.84, 2.51	
≥35	86	1.23	0.93, 1.64		25	1.28	0.76, 2.16	
HR[c] per 5 kg/m^2		1.05	0.98, 1.12			1.05	0.92, 1.19	
BMI[d] at 50 years of age				0.002				0.96
<18.5	18	1.52	0.94, 2.46		2	0.45	0.11, 1.84	
18.5–21.9	220	1.00	Referent		79	1.00	Referent	
22.0–22.9	102	1.06	0.84, 1.34		24	0.70	0.44, 1.10	
23.0–24.9	234	1.15	0.96, 1.39		69	0.93	0.67, 1.30	
25.0–27.4	194	1.19	0.98, 1.45		58	0.97	0.69, 1.37	
27.5–29.9	69	1.08	0.82, 1.42		19	0.70	0.41, 1.21	
30.0–32.4	52	1.24	0.91, 1.70		11	0.73	0.39, 1.38	
32.5–34.9	25	1.14	0.74, 1.74		11	1.40	0.74, 2.66	
≥35	48	1.82	1.31, 2.52		9	0.93	0.46, 1.89	
HR[c] per 5 kg/m^2		1.13	1.05, 1.23			1.00	0.85, 1.16	
BMI[d] at 35 years of age				0.01				0.69
<18.5	29	0.91	0.62, 1.35		14	1.40	0.81, 2.43	
18.5–21.9	416	1.00	Referent		137	1.00	Referent	
22.0–22.9	143	1.17	0.97, 1.42		34	0.86	0.59, 1.25	
23.0–24.9	190	1.06	0.89, 1.26		49	0.81	0.58, 1.13	
25.0–27.4	106	1.15	0.92, 1.43		27	0.87	0.57, 1.34	
27.5–29.9	36	1.38	0.98, 1.94		9	1.05	0.53, 2.06	
30.0–32.4	23	1.41	0.92, 2.15		3	0.37	0.09, 1.51	
≥32.5	19	1.48	0.92, 2.38		9	2.24	1.13, 4.43	
HR[c] per 5 kg/m^2		1.16	1.04, 1.30			1.05	0.84, 1.30	
BMI[d] at 18 years of age				0.14				0.46
<18.5	150	0.97	0.81, 1.16		49	1.09	0.79, 1.50	
18.5–21.9	553	1.00	Referent		168	1.00	Referent	
22.0–22.9	87	1.06	0.85, 1.33		24	0.94	0.61, 1.46	
23.0–24.9	89	0.89	0.71, 1.12		22	0.74	0.47, 1.16	
25.0–27.4	50	1.17	0.88, 1.57		13	0.96	0.54, 1.73	
27.5–29.9	17	1.44	0.89, 2.34		3	0.86	0.27, 2.69	
≥30.0	16	1.39	0.89, 2.33		3	0.92	0.29, 2.88	
HR[c] per 5 kg/m^2		1.11	0.96, 1.29			0.89	0.66, 1.21	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MVHR, multivariable hazard ratio.

[a] There were 4 women with synchronous colon and rectal cancers.

[b] Calculated using PROC PHREG in SAS, version 9.1. We took relative risk (used in the text) to be equivalent to HR. All analyses were adjusted for age (in the baseline hazard of the Cox regression) and the following covariates: race/ethnicity, educational level, physical activity level, smoking status, alcohol consumption, and use of menopausal hormone therapy.

[c] Calculated after excluding subjects whose BMI at a given age was less than 18.5.

[d] Weight (kg)/height (m)^2.

the baseline age (to approximate change during total adulthood). We calculated average adult BMI across the periods weighted by the differences in number of years between each age point. We chose cutpoints for weight-change categories that were comparable with published values (2–5) and expressed summary estimates per 0.5 kg/year for each sex, as this value could have practical utilization in public health practice.

In multivariate analyses, we adjusted for age, person-years, race/ethnicity, educational level, physical activity level, smoking, alcohol consumption, family history of CRC, and among women, menopausal hormone therapy (MHT) use. We also considered height- and energy-adjusted intakes of red meat, processed meat, saturated fat, dietary fiber, and calcium as potential confounders (28), but we did not retain those variables in the final model because they failed to substantially alter β coefficients (≥10%) in our primary exposures.

Statistical analysis

We calculated person-years from the scan date of the risk-factor questionnaire in 1996 to the date of diagnosis of first primary CRC, death, or December 31, 2006, whichever came first. We used Cox regression to estimate hazard ratios and 95% confidence intervals of incident colon and rectal cancers (29).

As a pragmatic approach to modelling multiple associations, we assumed linear relations between BMI and risk (1) and, as a single outcome measure, assigned each BMI level its midpoint value and used the resulting discrete variable to report risk per each 5-kg/m^2 increase in BMI. We tested for linear trends using the Wald test. In weight-change analyses, models were adjusted for weight at the beginning of the change interval to account for differences in body size at the beginning of the interval.

We hypothesized that the standard World Health Organization definition of overweight with a lower BMI cutpoint of 25 (30) may fail to predict long-term CRC risk appropriately among young and middle-aged adults. Thus, we created the novel term "age-defined excess BMI" for young and middle-aged adults for which the lower BMI cutpoint differed according to age and sex. Specifically, we calculated the sex-specific means for distributions for these age groups and defined new lower cutpoints of excess BMI for ages 18 and 35 years of 21.5 and 24.5 in men and 20.7 and 22.4 in women, respectively. All analyses were conducted using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina). All statistical tests were 2-sided.

RESULTS

Mean BMI values at baseline and ages 18, 35, and 50 years and weight changes for the respective periods are shown in Table 1. As detailed previously (26), men (mean baseline age = 63.0 years) and women (mean baseline age = 62.6 years) with elevated baseline BMI were more likely to be physically inactive and to have high red meat consumption, but they were less likely to be current smokers and, among women, to have ever used MHT compared with those in normal BMI categories (Web Table 1). The correlation coefficients between BMI at baseline and BMI at ages 50, 35, and 18 years were 0.81, 0.58, and 0.37, respectively, in men and 0.82, 0.63, and 0.34, respectively, in women. BMI at baseline was positively correlated with weight gain since age 18 years in men ($r = 0.69$) and in women ($r = 0.84$) (Web Table 2).

We additionally tabulated baseline characteristics by weight change categories (Web Table 3). For men and women, compared with stable weight (defined as a change between −0.5 and 0.5 kg/year), individuals in categories with increased weight gain (0.5–0.9, 1.0–2.0, and >2.0 kg/year) were more likely to be younger and past smokers and to have high red meat consumption. They were less likely to be physically active and have a higher educational level. We evaluated the validity of assessing BMI at younger ages using recalled weight and height by comparing these against age- and sex-specific BMI distributions in contemporaneous populations and found broad agreement (Web Figures 1 and 2).

During 2,509,662 person-years of follow-up through 2006, we ascertained 4,076 incident colorectal cancers that originated in the colon in 3,032 subjects (2,070 in men, 962 in women) and in the rectum in 1,044 subjects (762 in men, 282 in women). There were 32 subjects (28 men, 4 women) who had primary cancers in both the colon and rectum.

Considering the total CRC incidence, in men, an increased risk was associated with BMI at baseline (per 5-kg/m^2 increase in BMI, hazard ratio (HR) = 1.14, 95% confidence interval (CI): 1.08, 1.20), BMI at age 50 years (per 5-kg/m^2 increase in BMI, HR = 1.15, 95% CI: 1.08, 1.22), and BMI at age 35 years (per 5-kg/m^2 increase in BMI, HR = 1.12, 95% CI: 1.04, 1.19) but not BMI at age 18 (Web Table 4). No clear associations between BMI and CRC incident risk emerged at any age for women.

Among men, we found increased incident risks of colon cancer per 5-kg/m^2 increase in weight in an inverse stepwise manner at baseline age (HR = 1.18, 95% CI: 1.11, 1.25), age 50 years (HR = 1.18, 95% CI: 1.10, 1.26), and age 35 years (HR = 1.16, 95% CI: 1.07, 1.25) but less so at age 18 years (HR = 1.10, 95% CI: 1.00, 1.20) (Table 2). Associations were comparable for distal and proximal colon cancer with BMI at baseline, at age 50 years, and at age 35 years. BMI at age 18 years was positively related to risk of distal colon cancer (HR = 1.18, 95% CI: 1.02, 1.36) but showed no association with proximal colon cancer (HR = 1.02, 95% CI: 0.90, 1.17) (Web Table 5). There were no associations with rectal cancer. Among women, statistically significant associations with colon cancer occurred in testing for trends across BMI categories only at age 50 years (HR = 1.13, 95% CI: 1.05, 1.23) and age 35 years (HR = 1.16, 95% CI: 1.04, 1.30) (Table 3) (Web Table 6).

In men, weight gains from the ages of 18 to 35 years and from age 18 years to age at baseline were consistently associated with increased risk of colon cancer but not of rectal cancer (except for weight gain between the ages of 18 and 35 years) (Table 4). The hazard ratio of colon cancer per 0.5-kg/year increase in weight from ages 18 to 35 years

Table 4. Risk of Incident Colon and Rectal Cancer in Relation to Weight Change Over 3 Consecutive Age Intervals Among Men in the National Institutes of Health-AARP Diet and Health Study Cohort, 1995–1996

Age Interval and Weight Change	Colon Cancer				Rectal Cancer			
	No. of Cases	MVHR[a]	95% CI	*P* for Trend[b]	No. of Cases	MVHR[a]	95% CI	*P* for Trend[b]
18 to 35 years				<0.0001				0.02
≤−0.50 kg/year	24	0.84	0.56, 1.28		9	0.83	0.42, 1.65	
−0.49–0.50 kg/year	893	1.00	Referent		357	1.00	Referent	
0.51–1.00 kg/year	797	1.20	1.09, 1.32		266	0.98	0.83, 1.15	
1.01– 2.00 kg/year	315	1.31	1.15, 1.50		115	1.19	0.96, 1.47	
>2.00 kg/year	41	1.99	1.43, 2.75		15	1.85	1.10, 3.12	
HR per 0.5 kg/year[a]		1.18	1.11, 1.25			1.12	1.10, 1.23	
35 to 50 years				0.32				0.12
≤−0.50 kg/year	61	0.95	0.72, 1.24		33	1.47	1.02, 2.11	
−0.49–0.50 kg/year	1380	1.00	Referent		500	1.00	Referent	
0.51–1.00 kg/year	448	1.07	0.96, 1.20		155	1.02	0.85, 1.23	
1.01– 2.00 kg/year	166	1.09	0.92, 1.29		63	1.14	0.87, 1.49	
>2.00 kg/year	15	0.95	0.56, 1.61		11	1.77	0.94, 3.33	
HR per 0.5 kg/year[a]		1.03	0.97, 1.10			1.08	0.98, 1.20	
50 years to baseline				0.02				0.49
≤−0.50 kg/year	125	0.87	0.71, 1.06		53	1.12	0.83, 1.51	
−0.49–0.50 kg/year	1371	1.00	Referent		501	1.00	Referent	
0.51–1.00 kg/year	345	1.02	0.90, 1.15		121	0.96	0.78, 1.18	
1.01– 2.00 kg/year	182	1.25	1.06, 1.47		66	1.08	0.82, 1.42	
>2.00 kg/year	47	1.22	0.91, 1.65		21	1.25	0.79, 1.99	
HR per 0.5 kg/year[a]		1.05	1.01, 1.10			1.02	0.95, 1.10	
18 years to baseline				<0.0001				0.25
≤−0.50 kg/year	4	0.92	0.34, 2.49		2	1.28	0.31. 5.26	
−0.49–0.50 kg/year	1346	1.00	Referent		497	1.00	Referent	
0.51–1.00 kg/year	626	1.21	1.10, 1.34		235	1.16	0.98, 1.37	
1.01– 2.00 kg/year	93	1.55	1.24, 1.93		28	1.11	0.75, 1.66	
>2.00 kg/year	1	1.14	0.16, 8.13		0	N/A		
HR per 0.5 kg/year[a]		1.29	1.16, 1.43		1.11	1.11	0.93, 1.33	

Abbreviations: CI, confidence interval; HR, hazard ratio; MVHR, multivariable hazard ratio; N/A, not applicable.

[a] All analyses were adjusted for age (in the baseline hazard of the Cox regression) and the following covariates: race/ethnicity, educational level, physical activity level, smoking status, alcohol consumption, and weight at the start of each time period.

[b] Calculated after excluding subjects whose average yearly weight gain was negative.

was 1.18 (95% CI: 1.11, 1.25), and from age 18 to age at baseline it was 1.29 (95% CI: 1.16, 1.43). Relations with weight gain during these age periods were comparable when examined by anatomic subsite (Web Table 7). There were no clear associations between weight gain from age 35 years to age 50 years or from age 50 years to age at baseline for colon cancer or colon cancer by anatomic subsite. In women, there were no consistent associations between weight gain during various age periods and the risk of colon cancer, colon cancer by anatomic subsite, or rectal cancer (except for borderline significant associations with colon and proximal colon from ages 18 to 35 years) (Table 5) (Web Table 8).

We tested the hypothesis that long-term weight loss (as a proxy of calorie restriction) is associated with reduced CRC risk, but the numbers of cases with adult weight loss (≥0.5 kg/year loss) were generally small. Notwithstanding, adult weight loss was largely unrelated to the risk of colon or rectum cancer in men or women compared with stable weight (Tables 4 and 5). The lack of association of weight loss with colon or rectal cancer risk was consistent across the entire lifetime and by colonic subsites. To confirm that weight loss due to preclinical disease did not account for the null associations observed, we repeated analyses in relation to weight change over the 3 consecutive age intervals after excluding colon cancer cases diagnosed within

Table 5. Risk of Incident Colon and Rectal Cancer in Relation to Weight Change Over 3 Consecutive Age Intervals Among Women in the National Institutes of Health-AARP Diet and Health Study Cohort, 1995–1996

Age Interval and Weight Change	Colon Cancer				Rectal Cancer			
	No. of Cases	MVHR[a]	95% CI	*P* for Trend[b]	No. of Cases	MVHR[a]	95% CI	*P* for Trend[b]
18 to 35 years				0.02				0.95
≤−0.50 kg/year	33	0.96	0.66, 1.41		6	0.56	0.22, 1.42	
−0.49–0.50 kg/year	675	1.00	Referent		208	1.00	Referent	
0.51–1.00 kg/year	206	1.14	0.97, 1.34		53	0.92	0.67, 1.26	
1.01– 2.00 kg/year	42	1.19	0.87, 1.64		15	1.32	0.77, 2.29	
>2.00 kg/year	6	2.62	1.17, 5.85		0			
HR per 0.5 kg/year[a]		1.14	1.02, 1.28			1.00	0.81, 1.25	
35 to 50 years				0.30				0.35
≤−0.50 kg/year	20	1.05	0.67, 1.64		5	0.77	0.29, 2.09	
−0.49–0.50 kg/year	647	1.00	Referent		186	1.00	Referent	
0.51–1.00 kg/year	202	1.06	0.90, 1.25		59	1.09	0.81, 1.47	
1.01– 2.00 kg/year	72	0.95	0.74, 1.22		29	1.30	0.86, 1.97	
>2.00 kg/year	21	1.77	1.14, 2.76		3	0.92	0.29, 2.90	
HR per 0.5 kg/year[a]		1.04	0.96, 1.13			1.07	0.93, 1.24	
50 years to baseline				0.36				0.48
≤−0.50 kg/year	47	1.02	0.74, 1.40		1	0.58	0.08, 4.14	
−0.49–0.50 kg/year	597	1.00	Referent		712	1.00	Referent	
0.51–1.00 kg/year	187	0.96	0.82, 1.14		205	0.99	0.84, 1.16	
1.01– 2.00 kg/year	98	0.90	0.72, 1.12		43	1.21	0.87, 1.66	
>2.00 kg/year	33	0.92	0.63, 1.34		1	2.07	0.29, 14.79	
HR per 0.5 kg/year[a]		0.97	0.92, 1.03			1.04	0.92, 1.18	
18 years to baseline				0.48				0.16
≤−0.50 kg/year	1	0.58	0.08, 4.14		0	N/A		
−0.49–0.50 kg/year	712	1.00	Referent		196	1.00	Referent	
0.51–1.00 kg/year	205	0.99	0.84, 1.16		75	1.28	0.97, 1.69	
1.01– 2.00 kg/year	43	1.21	0.87, 1.66		11	1.16	0.62, 2.17	
>2.00 kg/year	1	2.07	0.29, 14.79		0	N/A		
HR per 0.5 kg/year[a]		1.04	0.92, 1.18			1.17	0.94, 1.45	

Abbreviations: CI, confidence interval; HR, hazard ratio; MVHR, multivariable hazard ratio; N/A, not applicable.

[a] All analyses were adjusted for age (in the baseline hazard of the Cox regression) and the following covariates: race/ethnicity, educational level, physical activity level, smoking status, alcohol consumption, and use of menopausal hormone therapy, and weight at the start of each time period.

[b] Calculated after excluding subjects whose average yearly weight gain for a given time period was negative.

2 years of cohort entry and found that risk estimates remained essentially unchanged (Web Table 9).

An exploratory analysis for the age-defined excess BMI throughout adulthood is shown in Table 6. Expressed as hazard ratio per 1-kg/m^2 anytime BMI excess, the association was statistically significant for colon cancer in men (HR = 1.04, 95% CI: 1.02, 1.06), with comparable associations noted for the distal and proximal subsites (Web Table 10). No association was observed for rectal cancer, and relations for women were null. We tested whether the presence of overweight or obesity per se impacted this association, but no associations were noted when individuals who were overweight or obese at 18 years of age were analyzed separately (Web Table 11).

We tested for interactions between age and weight changes by incident cancer subsites over the 3 consecutive age intervals among men and women and found no significant interactions (Web Table 12). We additionally tested for interactions between sex and weight changes because, as we have previously noted for associations with baseline BMI (1), we found significant differences for associations with incident colon cancer risk by sex for the periods of age 50 years to baseline ($P = 0.001$) and age 18 years to baseline ($P = 0.002$). Sex differences were strongest for incident proximal colon cancer (Web Table 13).

To address the possibility that the weak associations observed in women may be partly explained by MHT use, we undertook secondary analyses that stratified on the basis of

Table 6. Risk of Incident Colon and Rectal Cancer in Relation to Elevated Body Mass Index Across the Lifetime Among Men and Women in the National Institutes of Health-AARP Diet and Health Study Cohort, 1995–1996

Adulthood Excess BMI[a]	Colon Cancer				Rectal Cancer			
	No. of Cases	MVHR[b]	95% CI	*P* for Trend[c]	No. of Cases	MVHR[b]	95% CI	*P* for Trend[c]
Men				<0.0001				0.53
<18.5	6	0.85	0.38, 1.89		4	1.46	0.54, 3.91	
0	826	1.00	Referent		320	1.00	Referent	
≤1	310	1.04	0.91, 1.19		115	0.98	0.79, 1.22	
>1–2	273	1.13	0.98, 1.30		100	1.04	0.83, 1.31	
>2–4	338	1.12	0.98, 1.28		122	0.98	0.79, 1.21	
>4–6	180	1.33	1.13, 1.57		53	0.94	0.70, 1.28	
>6	137	1.41	1.17, 1.70		48	1.22	0.89, 1.66	
HR per kg/m^2 excess BMI[c]		1.04	1.02, 1.06			1.01	0.98, 1.04	
Women				0.021				0.98
<18.5	14	1.30	0.76, 2.22		6	1.73	0.76, 3.93	
0	457	1.00	Referent		142	1.00	Referent	
≤1	134	1.18	0.97, 1.43		38	1.05	0.73, 1.51	
>1–2	85	0.99	0.78, 1.25		24	0.88	0.57, 1.36	
>2–4	124	1.08	0.88, 1.33		36	0.89	0.60, 1.31	
>4–6	65	1.10	0.84, 1.44		14	0.80	0.46, 1.40	
>6	83	1.38	1.08, 1.76		22	1.18	0.75, 1.88	
HR per kg/m^2 excess BMI[c]		1.03	1.00, 1.05			1.00	0.96, 1.04	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MVHR, multivariable hazard ratio.

[a] Excess BMI (weight (kg)/height (m)^2) was defined in men as average BMI of >21 at 18 years of age, >24.5 at 35 years of age, >25 at 50 years of age, and >25 at current age. Among women, it was defined as average of BMI of >20.7 at 18 years of age, >22.4 at 35 years of age, >25 at 50 years, and >25 at current age. Subjects with a BMI at entry that was <18.5 were placed in a separate category regardless of excess BMI (all had to have had a negative value for excess BMI).

[b] All analyses were adjusted for age (in the baseline hazard of the Cox regression) and the following covariates: race/ethnicity, educational level, physical activity level, smoking status, alcohol consumption, and for women, use of MHT. There was no adjustment for initial BMI or height.

[c] Calculated after excluding subjects whose average yearly weight gain for a given time period was negative.

the latter. Among current MHT users, the risk of total CRC was positively associated with BMI at baseline (per 5-kg/m^2 increase in BMI, HR = 1.13, 95% CI: 1.01, 1.26), whereas BMI at baseline was unrelated to CRC risk among former MHT users (HR = 1.02, 95% CI: 0.83, 1.26) or among MHT never users (HR = 0.97, 95% CI: 0.89, 1.06; *P* value for the test of interaction = 0.02 for comparison of MHT current versus MHT former or never users).

In weight-change analyses, models that were adjusted for weight at the beginning of the change interval (as done here) may lead to parameter estimates that do not reflect the impact of the exposure of interest (31). We therefore repeated analyses of weight change that were unadjusted for weight at the beginning of the interval and found that our conclusions remain unaffected (Web Table 14).

DISCUSSION

In the present large prospective study of men and women, we showed that the following were significantly positively associated with colon cancer in men: 1) BMI at baseline, age 50 years, and age 35 years; 2) weight gain from ages 18 to 35 years and from age 18 years to baseline age; and 3) age-defined anytime excess BMI. Associations were generally similar for distal and proximal colon cancers. Among women, we found weaker or null associations between BMI and the risk of colon cancer. We found no consistent relations between BMI at various ages, weight gain, or age-defined anytime BMI excess and rectal cancer. Taken together, these findings suggest that excess body weight at numerous stages during adulthood and weight gains during early to middle adulthood have important influences on colon cancer risk, relations that are more consistent among men than among women. We found no relation between adult weight loss and the risk of colon or rectal cancers.

Our previous meta-analysis of 29 cohorts found that BMI is positively associated with both colon and rectal cancers in men but only colon cancer in women (1). In the present analysis, we similarly found that the strongest

associations were for colon cancer risk in men. One possible explanation for the weaker associations observed in women is that waist circumference or waist-to-hip ratio as approximations of central obesity may represent more informative CRC risk predictors than BMI in women (32, 33), and this is the subject of ongoing study.

We noted that in men, associations for weight gain at different age periods were comparable for distal and proximal colon cancers. Our findings regarding weight gain at different age periods differ from those of the Health Professionals Follow-up Study, which found stronger associations for weight change with proximal (per 4.52-kg increase over 2 years, HR = 1.39) over distal (HR = 0.96) colon cancer (22). Many individuals with excess body weight are hyperinsulinemic, and some studies suggest that associations with hyperinsulinemic states are limited to proximal colon cancer or adenoma (34, 35) or are stronger for the proximal colon than for the distal colon (36). By contrast, BMI tends to be more strongly associated with microsatellite stable than microsatellite instable colorectal tumors (25), and microsatellite stable tumors are predominantly distally located. Consistent with this, the Norwegian Countries Study recently reported stronger associations with BMI for distal compared with proximal colon cancer (37). As an explanation of these inconsistencies, we have shown that incidence of left-sided colonic cancer predominate in the ages 50–70 years, whereas that of right-sided cancer predominates after the age of 70 years (38). Thus, the age setting of analysis may influence the observed BMI-cancer sub-site associations.

For women, we noted no associations between weight gain and risk of either colon or rectal cancer. Similarly, null associations were observed in participants from the Nurses' Health Study (23), women from the Colon Cancer Family Registry (25), and participants in a population-based Canadian study (39). As the present analysis notes, the BMI-CRC associations may be modified by MHT history (in the direction opposite that of the MHT effect modification seen between BMI and risk of postmenopausal breast and endometrial cancers (40)) and requires further research.

Consistent with findings from the Health Professionals Follow-up Study (22), we found no significant association with weight loss, though numbers of cancers were small. This contrasts with breast cancer, in which decreased postmenopausal breast cancer risk is observed with weight loss in middle adulthood (10) and with sustained weight loss after menopause (4). Success in detecting an association with weight loss in such studies may reflect a more rigorous definition of stable weight, repeated assessments of weight change across successive questionnaire cycles (as done in the Nurses' Health Study (4)), and/or longer follow-up. Interestingly, recent studies of patients undergoing bariatric surgery for morbid obesity (a model of sustained weight loss over 10 years) point to a reduction in cancer restricted to women, in whom breast and endometrial cancers are the major proportion of obesity-related malignancies, but not in men, in whom colon cancers are more prevalent (41).

Although adult weight gain and BMI at baseline were positively correlated in our data, positive trends in men remained for weight gain when weight at the start of each age period was modelled simultaneously, suggesting that adult weight gain (at any time) is an important risk factor for colon cancer in men. This may point to yet not fully understood age-related metabolic changes underpinning biologic mechanisms. Similar observations were noted for associations with colorectal cancer in older women (24) and in renal cancer risk (42). We speculate that increased BMI in individuals in early adulthood does not yet manifest as overt insulin resistance, but it does signal a trajectory to a hyperinsulinemic state in later adulthood, which does predict for colon cancer development.

Our findings have implications for public health cancer prevention strategies. First, our results support the existing literature that BMI more strongly impacts colon cancer risk in men than in women (43) and an emerging theme that cancer prevention should be sex- and age-targeted (44). Second, avoidance of weight gain needs to be emphasized throughout adulthood, rather than targeting BMI reduction in late adulthood.

There are potential study limitations. First, the height and weight were self-reported, which may bias (overestimate) BMI-cancer associations, but the impact of such bias is uncertain. The lack of a strong association in women and the generally modestly elevated risks observed in men suggests that this was not a substantial problem in our analyses. Second, determinations of BMI at ages 18, 35, and 50 years depend upon long-term recall of weight from an earlier time in life. We tested BMI distributions of our study against population data contemporaneous with our population for the respective age strata and found similar BMI parameters, suggesting the lack of a serious recall problem. Third, our findings on associations with BMI at ages 18 and 35 years may not be generalizable to today's populations, as BMI distributions for equivalent age groups have shifted to the right (45).

Strengths of the present study include its large size, prospective design, colonic subsite classification, and detailed anthropometry data across a substantial range in BMI levels. The latter enabled us to examine CRC risk according to narrow BMI categories with enhanced precision and to explore linear relations across the BMI range. We addressed changes in weight across adulthood in 3 ways: 1) associations with BMI at each age point; 2) associations with a weight gain of 0.5 kg/year; and 3) a novel model using age-defined excess weight. We undertook extensive tests of interactions and sensitivity analyses and found our models to be consistent. To our knowledge, this is the first prospective study to examine weight change throughout the entire adulthood among both men and women for both colon and rectal cancer.

Important questions remain regarding how to best quantify the cumulative effects of excess body weight over several decades, the differential effect of key weight change periods during the life course, and interactions with other risk factors. The ideal study to assess the effects of weight change over time on CRC risk would be a longitudinal repeated measurement study commencing in early adulthood. The statistical handling of these data would be complex and computationally demanding. Finally, it remains to be seen whether preventing weight gain and/or reducing BMI via effective interventions in adult populations reduces

CRC risk and forms the basis for public health strategies to prevent CRC worldwide.

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