Systematic Reviews and Meta- and Pooled Analyses

Weight Change and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis

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Results from cohort studies of adult weight gain and risk of colorectal cancer are inconsistent. We conducted a systematic review and meta-analysis of prospective studies assessing the association of change in weight/body mass index with colorectal cancer risk. We searched Scopus and Web of Science up to June 2014 and supplemented the search with manual searches of the reference lists of the identified articles. Thirteen studies published between 1997 and 2014 were pooled by using a random-effects model, and potential heterogeneity was explored by fitting meta-regression models. The highest weight gain category, measured by weight/body mass index, compared with a reference category, was associated with increased risk of colorectal cancer (hazard ratio (HR) = 1.16, 95% confidence interval (CI): 1.08, 1.24), whereas no association was found for weight loss (HR = 0.96, 95% CI: 0.89, 1.05). There was no suggestion of heterogeneity across studies. For dose response, a 5-kg weight gain was associated with a slightly increased risk of colorectal cancer (HR = 1.03, 95% CI: 1.02, 1.05), with some heterogeneity observed (I^2 = 42%; P = 0.02), which was partially explained by sex (ratio of HRs = 1.03, 95% CI: 1.00, 1.07). In this meta-analysis, gain in weight/body mass index was positively associated with colorectal cancer risk.

colorectal cancer; meta-analysis; systematic review; weight gain; weight loss

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.

There is convincing epidemiologic evidence for an association between excess body fat, commonly measured by weight or body mass index (weight (kg)/height (m)^2), and increased risk of colorectal cancer (1–3). A stronger association has been reported for abdominal obesity, measured by waist circumference, with an estimated 50% greater risk of colorectal cancer in the highest category of waist circumference (4, 5). This suggests that excess abdominal fat is more strongly associated with risk of colorectal cancer than overall obesity.

In addition to current weight and abdominal obesity, there is growing evidence suggesting that adult weight gain and increasing abdominal obesity increase the risk for colorectal cancer (6). Most studies that have examined the association between weight change and the risk of colorectal cancer have investigated changes between early adulthood (e.g., ages 18 or 21 years) and mid- or later life (7–10), in which weight at young adulthood was recalled. The few studies that have assessed weight change over shorter time frames have inconsistent results (11–13).

To our knowledge, there is no published systematic review and meta-analysis of studies assessing the association between change in weight or waist circumference, measured retrospectively or prospectively, and the risk of colorectal cancer. The aim of this review was to systematically examine the evidence from prospective studies of adults on the association between change in weight or waist circumference and the risk of colorectal cancer and to quantify this association by using meta-analysis.

METHODS

Search strategy

A literature search was carried out in Scopus (Elsevier, Inc., New York, New York) and Web of Science (Science Citation Index Expanded and Social Sciences Citation Index and Arts & Humanities Citation Index; Thomson Reuters, New York, New York) to identify studies that assessed the

association between change in weight, body mass index, or waist circumference and risk of colorectal cancer. We identified English language papers published before June 30, 2014, using the following search terms: ("anthropometry" OR "weight" OR "body mass index" OR "waist circumference" OR "hips circumference") AND ("prospective" OR "cohort") AND ("colorectal cancer" OR "colon cancer" OR "rectal cancer") AND ("aged" OR "adult"). Next, we completed a hand search of the bibliographies of retrieved papers to identify any further relevant studies. Finally, we carried out a further search of cohort studies included in the review by Renehan et al. (2) to ensure that any known cohort studies were not missed in the search. We did not include informally published written material or unpublished studies. This systematic review was planned, conducted, and reported in adherence to the standards of quality for reporting meta-analyses of observational studies (14).

Eligibility criteria

Studies were eligible if they met the following criteria: 1) prospective studies; 2) English language; 3) adults (men and/or women); 4) reports of results for change in weight, body mass index, or waist circumference ascertained either from early adulthood (e.g., aged 18 or 21 years) to midlife or from midlife to older age; 5) the outcome of interest was colorectal, colon, or rectal cancer; and 6) the study reported enough information to extract hazard ratio estimates and the corresponding 95% confidence intervals. Data on the hazard ratio of colorectal cancer and its associated 95% confidence interval were extracted for all subgroups presented by the authors (e.g., men and women). If results from a single study were reported more than once, we included the most recent report.

Data extraction

The following data were extracted from each report: the first author's last name, year of publication, name of the study, country where the study was performed, participants' sex, sample size at baseline, whether change in weight or waist circumference was reported including details of the assessment (i.e., directly measured or self-reported), categories of the exposure measure (if presented), hazard ratio and corresponding 95% confidence interval, potential confounders adjusted for in the analysis, numbers of cases, and corresponding person-years. We extracted the hazard ratios from the most fully adjusted model in each study. If results were reported for 2 multivariable models, we extracted hazard ratios from the models that did not adjust for possible intermediaries in the causal pathway (e.g., diabetes mellitus or cancer).

Data analysis

A.K. reviewed all the abstracts and retrieved the full articles. A.K. and J.A.S. independently extracted the data from the included studies, and D.R.E. resolved any discrepancies. We estimated, using meta-analysis with random effects, the pooled hazard ratio for the highest and lowest categories of weight change versus the reference category (i.e., largest weight gain and weight loss, respectively), as well as the hazard ratio

for a dose-response relationship across the weight change categories.

Dose-response analysis

All of the studies presented hazard ratios for weight, but 3 of the studies presented the hazard ratio for body mass index (10, 13, 15). Of these 3 studies, the one by Hughes et al. (10) was the only study to present the participants' average height, which enabled us to convert the estimates to the corresponding change in weight. Next, for each study that did not present hazard ratios for a dose-response relationship (e.g., hazard ratio per unit change in weight), the category-specific hazard ratio estimates were combined to calculate the $\log_e$(hazard ratio) per 5-kg weight change (16, 17). For those papers where the category-specific mean/median weight change was not presented, we assigned the midpoint for each weight change category to the corresponding hazard ratio estimate. Further, for categories with no lower or upper bound (e.g., ≥5 kg), we assigned the midpoint between the cutoff value and the minimum or maximum values; if this information was not presented, we used the lower or upper limits of the 95% confidence interval. For studies that did not provide the numbers of cases and corresponding person-time within each weight change category, we estimated the dose-response relationship using variance-weighted least-squares regression analysis.

For the dose-response meta-analysis, we examined a potential nonlinear relationship between weight change and colorectal cancer by modeling weight change using restricted cubic splines (3 knots at fixed percentiles of 25%, 50%, and 75% of the distribution) and compared this model with a linear model using the likelihood ratio test.

We visually inspected a funnel plot of study size versus standard error and performed Egger's regression asymmetry test to ascertain bias due to small-study effects (18).

Statistical heterogeneity between studies was tested with the Q statistic and quantified with the I^2 statistic (19). To explore sources of study heterogeneity, we fitted meta-regression models to estimate the association between the log-transformed study-specific hazard ratios and the following prespecified variables: cancer site (colorectal, colon, or rectal); participants' sex; method used to measure weight (i.e., measured or self-reported); time frame for assessing weight change (i.e., from early adulthood to midlife or from midlife to older age); whether physical activity was adjusted for in the original analysis; and the proportion of the baseline sample included in the analysis.

Univariable and multivariable meta-regression analyses were conducted; the univariable meta-regression analyses were done to estimate the between-studies variance, τ^2. The τ^2 from the model without any covariates compared with the τ^2 from the models with each covariate added separately gives an indication of how much variation between the studies the covariate explains.

Sensitivity analyses

Two of the included studies used data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study (20, 21). Aleksandrova et al. (20) presented the

association between weight change from age 20 years to midlife (i.e., baseline) and the risk of colorectal cancer using data from the EPIC cohort. Steins Bisschop et al. (21) used a subset of the EPIC cohort, EPIC-PANACEA, and reported on weight change assessed at baseline (i.e., midlife) and again 5 years later. We conducted a sensitivity analysis excluding the study by Steins Bisschop et al. (21).

For the meta-analysis comparing the highest weight gain category with the reference group, 8 of the studies presented their results in categories with a large number of cases. However, Renehan et al. (7) had only 1 case of colon cancer in each sex for the highest category of change; we combined this group with the next highest category using the method of variance-weighted least squares (i.e., the hazard ratio corresponding to a change of >2.00 kg/year was combined with the hazard ratio corresponding to a change of 1.01–2.00 kg/year). We carried out a sensitivity analysis where we removed the estimates from this study.

The study by Oxentenko et al. (9) presented results from 2 models; the first adjusted for age at baseline, whereas the second adjusted for age at baseline, diabetes mellitus, and additional confounders. Because diabetes mellitus might be an intermediate on the causal pathway from weight change to colorectal cancer, we chose to include the first model (i.e., the model that adjusted only for baseline age). We conducted a sensitivity analysis where we excluded the estimates from the study by Oxentenko et al. (9).

Results are shown in the form of forest plots, the data are grouped by time frame for assessing weight change (i.e., from early adulthood to midlife and from midlife to older age) and,

within these groups, the data are sorted by cancer site and year of publication. Results for meta-regression analyses are presented in tables, as suggested by Higgins and Green (22).

All analyses were performed by using Stata, version 13, statistical software (23).

RESULTS

Study selection

A total of 1,494 articles were identified via Scopus and Web of Science searches. Of these, 326 duplicate articles were excluded, and a further 1,116 articles were excluded on the basis of their title and abstract, leaving 52 articles for further evaluation. After obtaining the full articles, we excluded a further 39 papers, leaving 13 articles appropriate for the meta-analysis. The reasons for excluding studies are outlined in Figure 1; the majority of the excluded papers did not present results for change in weight or waist circumference (36%), or the incidence of colorectal cancer was not the outcome of interest (59%).

Study characteristics

Table 1 shows a summary of the characteristics of the studies eligible for inclusion in the meta-analysis. Seven studies were conducted in Europe (10, 12, 13, 15, 20, 21, 24), 5 in the United States (7, 9, 11, 25, 26), and 1 in Australia (8). All studies examined change in weight ($n = 10$) (7–9, 11, 12, 20, 21, 24–26) or body mass index ($n = 3$) (10, 13, 15) as
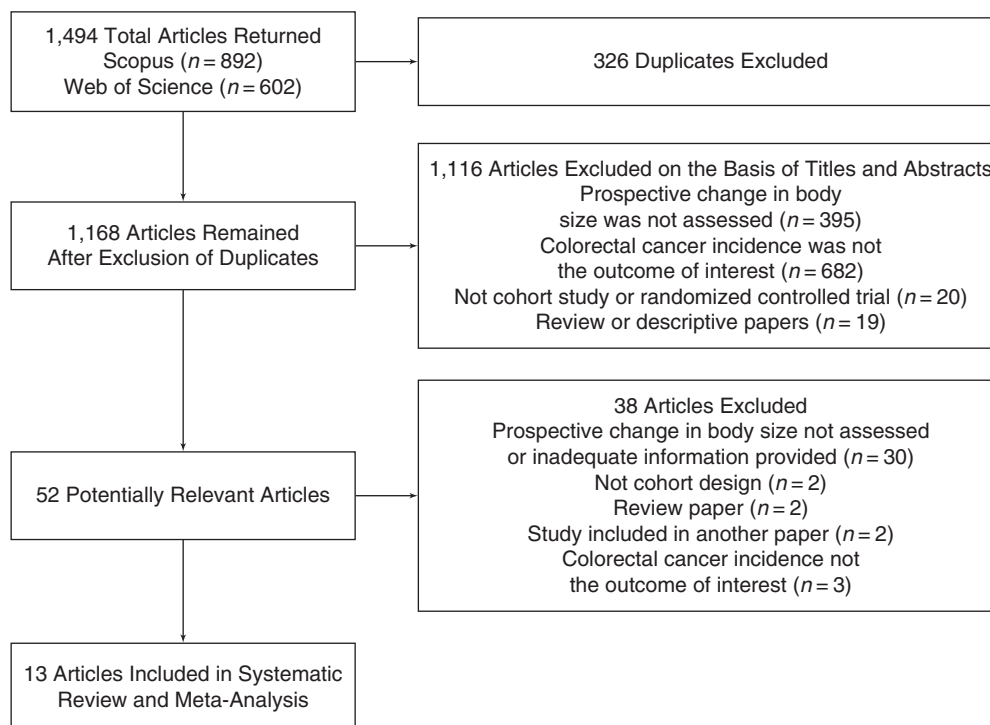

Figure 1.   Selection of studies for inclusion in a meta-analysis of weight change and risk of colorectal cancer, 1974–2014.

Table 1. Characteristics of Prospective Studies on Change in Weight or Body Mass Index and Risk of Colorectal Cancer, 1997–2014

First Author, Year (Reference No.)	Cohort Name	Location	Proportion of Baseline Sample Included in Analysis, %	Body Size Measurement	Confounders	Time Frame for Body Size Change
Aleksandrova, 2013 (20)	European Prospective Investigation into Cancer and Nutrition	Europe	39	Weight	Age, weight at age 20 years, BMI at age 50 years, waist circumference, smoking status, alcohol intake, physical activity, education, diet (red and processed meat, fish and shellfish, fruits and vegetables, fiber)	Early adulthood to midlife
Bassett, 2010 (8)	Melbourne Collaborative Cohort Study	Australia	95	Weight	Age, weight at age 18 years, height at study entry, smoking status, alcohol intake, education, diet (processed and fresh red meat, fruit and vegetable intake, fat intake, daily energy intake), and country of birth	Early adulthood to midlife
Colditz, 1997 (25)	Nurses' Health Study	United States	52	Weight	Age, weight at age 18 years	Early adulthood to midlife
Han, 2014 (26)	Atherosclerosis Risk in Communities Study	United States	88	Weight	Age, BMI at age 25 years, height, smoking status at age 25 years, cigarette smoking status, alcohol intake, physical activity at baseline, education, and race-center	Early adulthood to midlife
Hughes, 2011 (10)	Netherlands Cohort Study	Netherlands	N/A	BMI	Age, BMI at age 20 years, BMI at baseline minus BMI at age 20 years, smoking status, alcohol intake, physical activity, socioeconomic status, total energy intake, and family history of colorectal cancer	Early adulthood to midlife
Laake, 2010 (12)	Norwegian Counties Study	Norway	66	Weight	Age, baseline BMI, height, smoking status, physical activity, education, energy intake, and country of birth	Midlife to older age
Larsson, 2006 (24)	Cohort of Swedish Men	Sweden	94	Weight	Baseline age, smoking, physical activity, education, family history of colorectal cancer, history of diabetes, and aspirin use	Early adulthood to midlife
Oxentenko, 2010 (9)	Iowa Women's Health Study	United States	88	Weight	Age at baseline	Early adulthood to midlife
Rapp, 2008 (13)	Vorarlberg Health Monitoring and Prevention Program	Austria	37	BMI	Age, baseline BMI, weight at start of each period, smoking status, alcohol intake, occupational group, and blood glucose	Midlife to older age
Renehan, 2012 (7)	NIH-AARP Diet and Health Study	United States	48	Weight	Age, smoking status, physical activity, education, and race	Early adulthood to midlife
Samanic, 2006 (15)	Swedish Foundation for Occupational Safety and Health of the Construction Industry	Sweden	30	BMI	Age, baseline BMI, smoking status, and calendar year	Midlife to older age
Steins Bisschop, 2014 (21)	EPIC-PANACEA	Europe	93	Weight	Age, BMI at recruitment, smoking, alcohol intake, education, diet (total dietary fiber, fruit and vegetables, fish and shellfish, red and processed meat), and time between weight assessments. For women: menopausal status, use of oral contraceptives, and use of hormone replacement therapy	Midlife to older age
Thygesen, 2008 (11)	Health Professionals Follow-up Study	United States	83	Weight	Age, smoking status, alcohol intake, physical activity, diet (meat, total calories, folate, methionine, vitamin D, calcium, total calorie, multivitamin), aspirin, endoscopic screening, and family history of colorectal cancer	Midlife to older age

Abbreviations: BMI, body mass index (weight (kg)/height (m)^2); EPIC, European Prospective Investigation into Cancer and Nutrition; N/A, not available; NIH, National Institutes of Health; PANACEA, Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating out of Home, and Obesity.

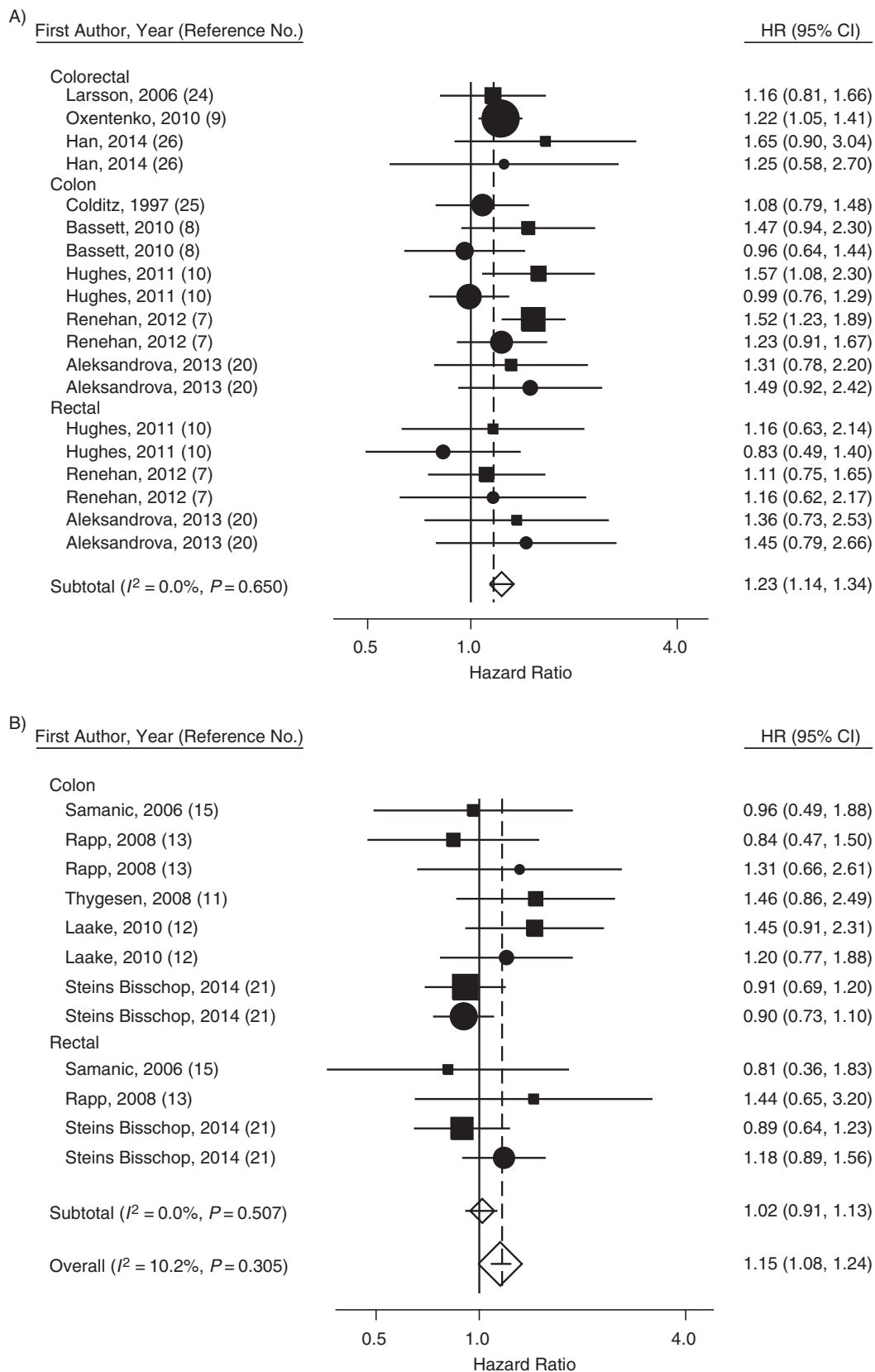**Figure 2.** Adjusted hazard ratio (HR) for the risk of colorectal cancer comparing the largest weight gain group with the reference group for change measured from early adulthood to midlife (A) and change measured from midlife to older age (B) for males (squares) and females (circles), 1997–2014. Overall estimate reflects a combined hazard ratio from parts A and B. Dashed line, overall estimate; bars, 95% confidence interval (CI).

Table 2. Results From Meta-Regression Analyses[a] of Weight Gain Compared With a Weight-Stable Group and Risk of Colorectal Cancer, 1997–2014

Covariate	No. of HRs	No. of Studies[b]	HR	95% CI	I^2, %	τ^2	Univariable			Multivariable		
							Ratio of HRs	95% CI	P Value	Ratio of HRs	95% CI	P Value
Model with no covariates	31	13	1.16	1.06, 1.26	10.2	0.012						
Cancer site												
Colorectal	4	3	1.24	1.00, 1.55	12.1	0.014	1.00	Referent		1.00	Referent	
Colon	17	10	1.16	1.04, 1.30			0.94	0.73, 1.19	0.580	0.85	0.65, 1.11	0.227
Rectal	10	6	1.09	0.91, 1.30			0.88	0.66, 1.16	0.344	0.82	0.60, 1.12	0.192
Sex												
Women	14	10	1.11	0.99, 1.25	7.9	0.011	1.00	Referent		1.00	Referent	
Men	17	11	1.21	1.07, 1.37			1.09	0.92, 1.29	0.286	1.07	0.91, 1.26	0.365
Time frame for reporting body size change												
Early adulthood to midlife	19	8	1.23	1.13, 1.35	0.0	0.003	1.00	Referent		1.00	Referent	
Midlife to older age	12	5	1.02	0.91, 1.16			0.83	0.71, 0.97	0.019	0.91	0.72, 1.22	0.524
Method used to collect body size at each wave												
Measured at baseline and follow-up wave(s)	7	3	1.15	0.90, 1.47	3.9	0.008	1.00	Referent		1.00	Referent	
Measured at baseline, self-reported at follow-up wave(s)	12	4	1.09	0.95, 1.23			0.95	0.72, 1.25	0.682	1.05	0.72, 1.53	0.780
Self-reported at baseline and follow-up wave(s)	12	6	1.22	1.09, 1.36			1.06	0.81, 1.39	0.669	0.99	0.66, 1.49	0.965
Adjusted for physical activity												
No	13	6	1.05	0.94, 1.18	0.0	0.007	1.00	Referent		1.00	Referent	
Yes	18	7	1.28	1.14, 1.43			1.21	1.03, 1.42	0.019	1.13	0.92, 1.38	0.226
Proportion of baseline sample included in analysis, %[c]												
<80	16	6	1.26	1.11, 1.43	0.0	0.007	1.00	Referent		1.00	Referent	
≥80	11	6	1.10	0.99, 1.21			0.87	0.74, 1.03	0.096	0.88	0.70, 1.10	0.252

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Meta-regression models are fitted assuming random effects, which allows for a variance component τ^2 that accounts for the unexplained heterogeneity between studies. Note, when there is little heterogeneity across the studies, fixed-effect and random-effects meta-analyses will give similar estimates.

[b] The number of studies exceeds the total in the categories of sex and cancer site because some studies presented results for the all subgroups (e.g., for both men and women).

[c] The number of studies is 12; Hughes et al. (10) used a case-cohort design, and it was not appropriate to compare the proportion included in that analysis with those of the traditional cohort designs.

the exposure of interest; none examined change in waist or hips circumference, and all presented results separately for men and women. Eight studies assessed change retrospectively by using self-reported weights in early adulthood (7–10, 20, 24–26) and, of these, 3 studies measured weight at baseline (8, 20, 26). Five studies assessed change prospectively (11–13, 15, 21); of these, 3 studies measured weight at both waves of data collection (12, 13, 15). Thygesen et al. (11) used self-reported weight assessments, recorded prospectively. Steins Bisschop et al. (21) measured weight at baseline and self-reported weight 5 years after baseline. Three studies presented results for colon and rectal cancers combined (9, 24, 26), 6 studies presented results separately for colon and rectal cancers (7, 10, 13, 15, 20, 21), and the remaining 4 studies presented results for colon cancer only (8, 11, 12, 25).

Web Table 1 available at http://aje.oxfordjournals.org/ shows the hazard ratios and corresponding 95% confidence intervals for each study for weight/body mass index change and the risk of colorectal cancer for the categorical and dose-response associations.

Largest category of weight gain compared with the reference category and the risk of colorectal cancer

Thirteen prospective studies were included in this meta-analysis and the multivariable-adjusted hazard ratios comparing the largest weight gain category with the reference category for each study, and all studies combined are presented in Figure 2. There was evidence of an increased risk of colorectal cancer for the largest weight gain group, such that the risk of colorectal cancer was 16% higher for those in the highest weight gain category compared with those in the reference group (hazard ratio (HR) = 1.16, 95% CI: 1.08, 1.24). Studies that assessed change from midlife to older age (Figure 2B) had a lower hazard ratio compared with studies examining change from early adulthood to midlife (Figure 2A) (ratio of HRs = 0.83, 95% CI: 0.71, 0.97; $P = 0.02$). Studies that included physical activity in the analysis had higher hazard ratios than studies that did not (ratio of HRs = 1.21, 95% CI: 1.03, 1.42; $P = 0.02$) (Table 2).

There was little heterogeneity across the studies ($I^2 = 10.2\%$, $P = 0.30$ from the χ^2 test for heterogeneity) (Table 2). There did not appear to be any small-study effects; the corresponding funnel plot appeared symmetrical (Figure 3), and there was weak evidence of small-study effects from Egger's regression asymmetry test ($P = 0.62$).

Weight loss compared with the reference category and the risk of colorectal cancer

Figure 4 shows the results for the meta-analysis comparing weight loss with the reference group. Of the 13 studies, 10 studies were included in this meta-analysis; 3 studies did not present results for a weight-loss group compared with a weight-stable or a reference group (9, 15, 25). There was no association between weight loss compared with a reference or stable group and the risk of colon or rectal cancer (HR = 0.96, 95% CI: 0.89, 1.05), regardless of whether change was assessed from early adulthood to midlife (Figure 4A) or from midlife to an
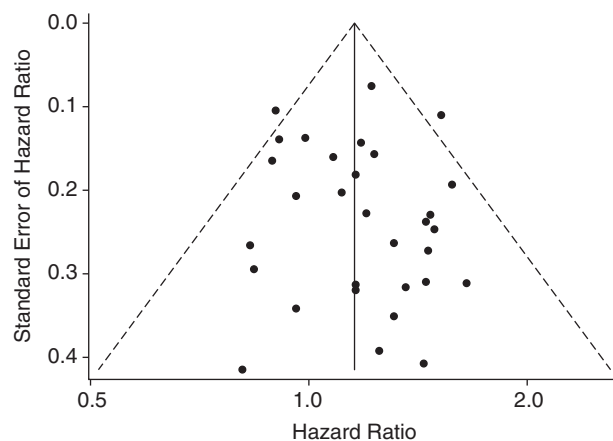

Figure 3. Funnel plot of the studies included in the meta-analysis comparing the largest weight gain group with the reference group for the risk of colorectal cancer, 1997–2014. The x-axis is on the log scale. Continuous line, no effect; dashed line, upper and lower 95% confidence limits.

older age (Figure 4B) (ratio of HRs = 1.05, 95% CI: 0.88, 1.26; $P = 0.55$).

There was little heterogeneity across the studies ($I^2 = 0.0\%$; $P = 0.71$ from the χ^2 test for heterogeneity) (Table 3). The funnel plot appeared symmetrical (Figure 5), and Egger's regression asymmetry test did not suggest the presence of small-study effects ($P = 0.30$).

Dose-response relationship for weight gain and risk of colorectal cancer

Nine studies were included in the dose-response analysis. Rapp et al. (13) and Samanic et al. (15) presented results for change in body mass index, but because they did not present the mean height, we were unable to convert the hazard ratios for change in body mass index to hazard ratios for change in weight. Colditz and Coakley (25) did not provide estimates for each category of weight change and, thus, a dose-response association could not be estimated. Han et al. (26) presented results for percent change, which could not be converted to an absolute change.

The pooled hazard ratio was 1.03 (95% CI: 1.02, 1.05) per 5-kg weight gain (Figure 6), with no evidence of departure from linearity ($P = 0.49$). The pooled hazard ratios for weight gain from early adulthood to midlife (Figure 6A) and from midlife to older age (Figure 6B) were similar (ratio of HRs = 1.03, 95% CI: 0.95, 1.12; $P = 0.51$). There was some heterogeneity across the estimates ($I^2 = 41.6\%$; $P = 0.02$ from the χ^2 test for heterogeneity).

Table 4 shows the results of the meta-regression analyses for the prespecified covariates. Slightly stronger associations were found for men than for women (ratio of HRs = 1.03, 95% CI: 1.00, 1.07; $P = 0.07$). The pooled hazard ratios did not vary by cancer site or the method used to ascertain weight.

Visual inspection of the funnel plot did not indicate the presence of small-study effects, and Egger's regression
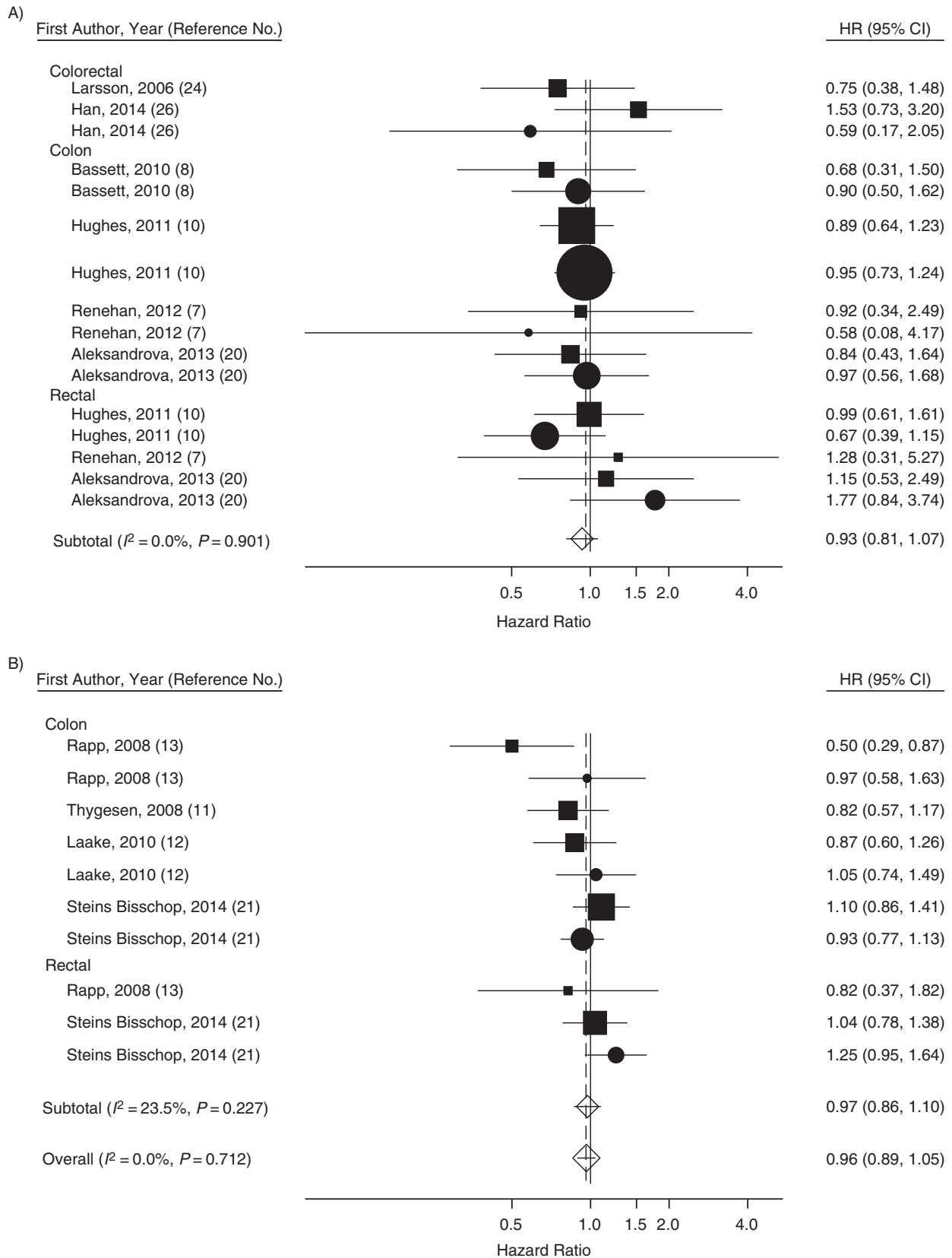
Figure 4. Adjusted hazard ratio (HR) for the risk of colorectal cancer comparing the largest weight loss group with the reference group for change measured from early adulthood to midlife (A) and change measured from midlife to older age (B) for males (squares) and females (circles), 1997–2014. Overall estimate reflects a combined hazard ratio from parts A and B. Dashed line, overall estimate; bars, 95% confidence interval (CI).

Table 3. Results From Meta-Regression Analyses[a] of Weight Loss Compared With a Weight-Stable Group and Risk of Colorectal Cancer, 1997–2014

Covariate	No. of HRs	No. of Studies[b]	HR	95% CI	I^2, %	τ^2	Univariable			Multivariable		
							Ratio of HRs	95% CI	P Value	Ratio of HRs	95% CI	P Value
Model with no covariates	26	10	0.96	0.88, 1.05	0.0	0.000						
Cancer site												
Colorectal	3	2	0.96	0.59, 1.57	0.0	0.000	1.00	Referent				
Colon	15	8	0.92	0.84, 1.02			0.96	0.58, 1.59	0.873	1.04	0.58, 1.86	0.898
Rectal	8	5	1.08	0.91, 1.28			1.13	0.67, 1.89	0.638	1.19	0.65, 2.18	0.553
Sex												
Women	11	8	0.99	0.88, 1.12	0.0	0.000	1.00	Referent		1.00	Referent	
Men	15	10	0.93	0.83, 1.06			0.94	0.79, 1.12	0.481	0.95	0.79, 1.14	0.564
Time frame for reporting body size change												
Early adulthood to midlife	16	6	0.93	0.80, 1.08	0.0	0.000	1.00	Referent		1.00	Referent	
Midlife to older age	10	4	0.98	0.88, 1.09			1.05	0.88, 1.26	0.547	1.08	0.78, 1.49	0.634
Method used to collect body size at each wave												
Measured at baseline and follow-up wave(s)	5	2	0.87	0.70, 1.08	0.0	0.000	1.00	Referent		1.00	Referent	
Measured at baseline, self-reported at follow-up wave(s)	12	4	1.04	0.93, 1.17			1.20	0.94, 1.53	0.143	1.21	0.74, 1.99	0.421
Self-reported at baseline and follow-up wave(s)	9	4	0.88	0.75, 1.03			1.01	0.77, 1.32	0.930	0.88	0.41, 1.86	0.717
Adjusted for physical activity												
No	9	3	0.99	0.88, 1.11	0.0	0.000	1.00	Referent		1.00	Referent	
Yes	17	7	0.93	0.82, 1.06			0.94	0.79, 1.11	0.456	1.30	0.88, 1.92	0.173
Proportion of baseline sample included in analysis, %[c]												
<80	12	4	0.93	0.77, 1.11	0.0	0.000	1.00	Referent		1.00	Referent	
≥80	10	5	0.98	0.89, 1.08			1.05	0.86, 1.29	0.595	1.11	0.66, 1.85	0.680

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Meta-regression models are fitted assuming random effects, which allows for a variance component τ^2 that accounts for the unexplained heterogeneity between studies. Note, when there is little heterogeneity across the studies, fixed-effect and random-effects meta-analyses will give similar estimates.

[b] The number of studies exceeds the total in the categories of sex and cancer site because some studies presented results for all the subgroups (e.g., for both men and women).

[c] The number of studies is 9; Hughes et al. (10) used a case-cohort design, and it was not appropriate to compare the proportion included in that analysis with those of the traditional cohort designs.
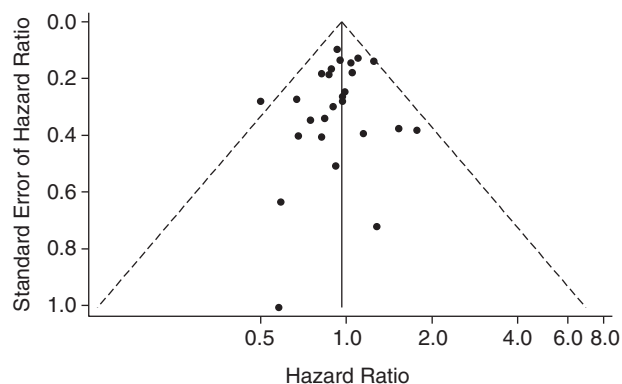
Figure 5. Funnel plot of the studies included in the meta-analysis comparing the largest weight loss group with the reference group for the risk of colorectal cancer, 1997–2014. The *x*-axis is on the log scale. Continuous line, no effect; dashed line, upper and lower 95% confidence limits.

asymmetry test did not suggest any small-study effects (*P* = 0.89) (Figure 7).

Sensitivity analyses

We conducted 3 sensitivity analyses where we excluded the estimates from the studies by Steins Bisschop et al. (21), Renehan et al. (7), and Oxentenko et al. (9); these did not change the results (data not shown).

DISCUSSION

The findings from this meta-analysis of 13 cohort studies showed that weight gain, measured by weight or body mass index, was associated with a moderately increased risk of colorectal cancer. There was a 16% increased risk of colorectal cancer with the highest category of weight gain compared with the reference category. Weight gain from early adulthood to midlife was associated with a higher risk of colorectal cancer than weight gain from midlife to older age, and studies that adjusted for physical activity had a higher risk of colorectal cancer than those that did not adjust for physical activity in their analysis. Weight loss, compared with the reference group, was not associated with the risk of colorectal cancer. A 5-kg weight gain was associated with a 3% increased risk of colorectal cancer, and the associations were slightly stronger for men than for women. We found very little heterogeneity across the studies.

Strengths and limitations

This meta-analysis was based on prospective cohort studies, which minimizes the possibility that the limitations of case-control studies have biased the results. Meta-analyses are limited by the potential of small-study effects, where smaller studies that do not find an association between weight change and risk of colorectal cancer do not publish their results. We used visual inspection of funnel plots and Egger's

regression asymmetry test to ascertain bias due to small-study effects (18). There did not appear to be any bias present from small-study effects; however, Egger's test is known to have low power when less than 20 studies are included in a meta-analysis (27).

We conducted several sensitivity analyses where we excluded the estimates reported from the following studies: Steins Bisschop et al. (21), Oxentenko et al. (9), and Renehan et al. (7). Steins Bisschop et al. (21) presented results from EPIC-PANACEA, a substudy of EPIC, Oxentenko et al. (9) adjusted for a possible intermediate in the causal pathway, and Renehan et al. (7) had only 1 case of colon cancer in each sex for the highest category of change; these exclusions did not change our results.

Our interest was in estimating the association between weight change and colorectal cancer. We combined the results from separate estimates for colon and rectal cancer using a random-effects model. This assumes that there is no within-study correlation between the estimates. This approach is consistent with previous meta-analyses looking at the risk of colorectal cancer (28, 29).

Meta-analysis is not able to adjust for confounders that were not included in the original analyses. By not adequately controlling for confounders, our findings might be biased in either direction (i.e., an exaggeration or underestimation of the risk estimate). Most studies adjusted for many confounders known to be associated with colorectal cancer. Strong evidence exists for an association between physical activity and the risk of colorectal cancer (3). Meta-regression analysis for the largest weight gain category compared with a reference group showed that studies that included physical activity in the analysis had higher hazard ratios for the risk of colorectal cancer than did studies that did not include physical activity in the analysis. As well, we found that studies that measured weight gain as the difference between weight at midlife and weight at a younger age had higher hazard ratios than those that measured weight gain from midlife to older age. Five of the 6 studies that adjusted for physical activity at baseline estimated the association between weight gain measured from early adulthood to midlife and the risk of colorectal cancer, suggesting that physical activity is a potential confounder of weight gain in early life.

Recalled weight in early life could introduce measurement error and lead to an attenuation of results between weight change and the risk of colorectal cancer. However, a number of validation studies have shown that current and recalled self-reported weight are highly correlated with measured data (30, 31).

Of the 13 studies included in the meta-analysis, 3 studies published results for body mass index. For the analysis of a dose-response association, we converted the change in body mass index to the corresponding change in weight. This conversion might have introduced additional uncertainty into our estimates. Only Hughes et al. (10) provided enough information for us to convert the change in body mass index to the corresponding change in weight; most adults reach their maximum height by the age of 21 years, and this remains constant through to midlife.

The use of the Newcastle-Ottawa scale and other scales for assessing study quality is controversial (32, 33), and this
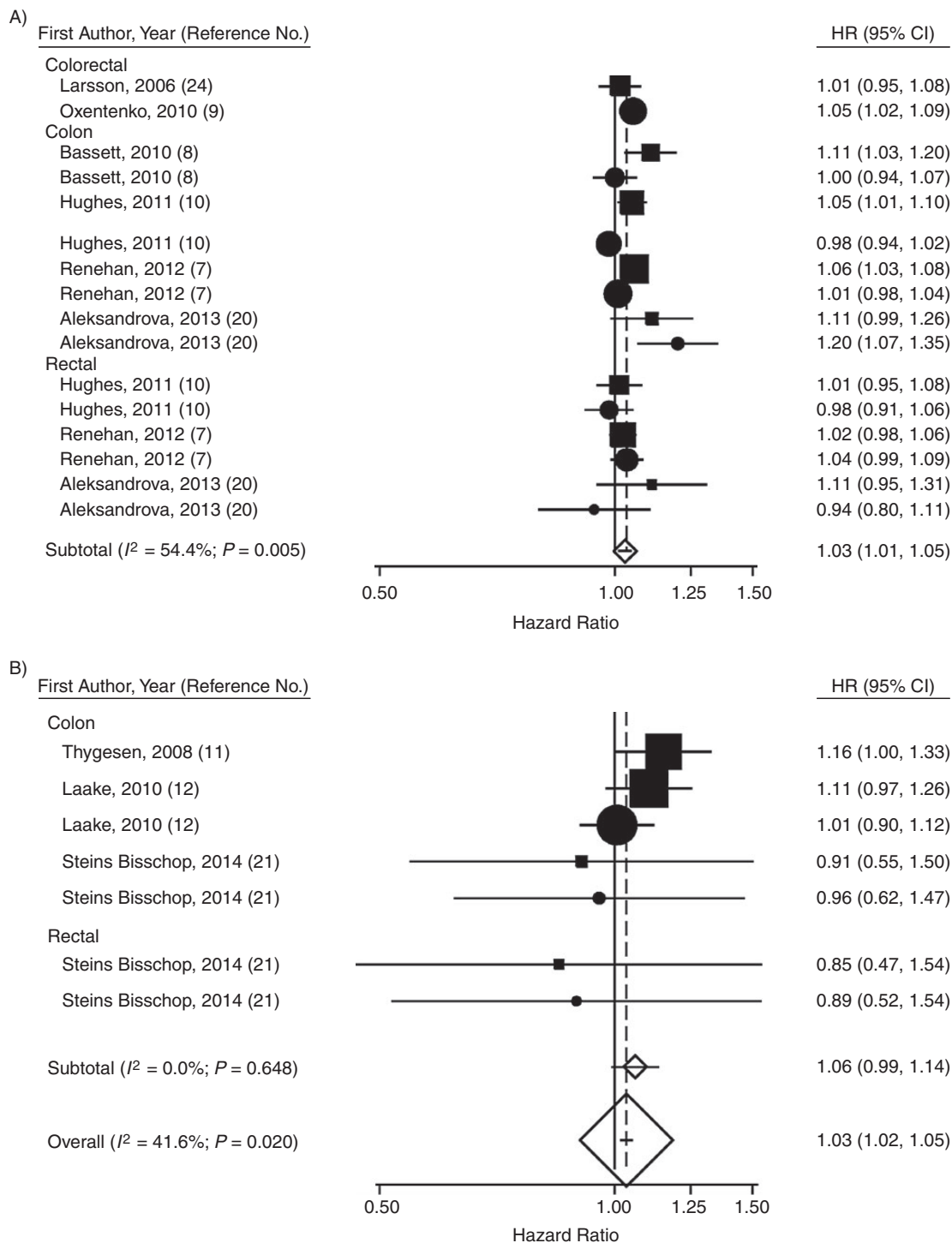
A)

First Author, Year (Reference No.)	HR (95% CI)
Colorectal	
Larsson, 2006 (24)	1.01 (0.95, 1.08)
Oxentenko, 2010 (9)	1.05 (1.02, 1.09)
Colon	
Bassett, 2010 (8)	1.11 (1.03, 1.20)
Bassett, 2010 (8)	1.00 (0.94, 1.07)
Hughes, 2011 (10)	1.05 (1.01, 1.10)
Hughes, 2011 (10)	0.98 (0.94, 1.02)
Renehan, 2012 (7)	1.06 (1.03, 1.08)
Renehan, 2012 (7)	1.01 (0.98, 1.04)
Aleksandrova, 2013 (20)	1.11 (0.99, 1.26)
Aleksandrova, 2013 (20)	1.20 (1.07, 1.35)
Rectal	
Hughes, 2011 (10)	1.01 (0.95, 1.08)
Hughes, 2011 (10)	0.98 (0.91, 1.06)
Renehan, 2012 (7)	1.02 (0.98, 1.06)
Renehan, 2012 (7)	1.04 (0.99, 1.09)
Aleksandrova, 2013 (20)	1.11 (0.95, 1.31)
Aleksandrova, 2013 (20)	0.94 (0.80, 1.11)
Subtotal (I^2 = 54.4%; P = 0.005)	1.03 (1.01, 1.05)

B)

First Author, Year (Reference No.)	HR (95% CI)
Colon	
Thygesen, 2008 (11)	1.16 (1.00, 1.33)
Laake, 2010 (12)	1.11 (0.97, 1.26)
Laake, 2010 (12)	1.01 (0.90, 1.12)
Steins Bisschop, 2014 (21)	0.91 (0.55, 1.50)
Steins Bisschop, 2014 (21)	0.96 (0.62, 1.47)
Rectal	
Steins Bisschop, 2014 (21)	0.85 (0.47, 1.54)
Steins Bisschop, 2014 (21)	0.89 (0.52, 1.54)
Subtotal (I^2 = 0.0%; P = 0.648)	1.06 (0.99, 1.14)
Overall (I^2 = 41.6%; P = 0.020)	1.03 (1.02, 1.05)

Figure 6. Adjusted hazard ratio (HR) for 5-kg weight gain and the risk of colorectal cancer for change measured from early adulthood to midlife (A) and change measured from midlife to older age (B) for males (squares) and females (circles), 1997–2014. Overall estimate reflects a combined hazard ratio from parts A and B. Dashed line, overall estimate; bars, 95% confidence interval (CI).

controversy is also mentioned in the standards of quality for reporting meta-analyses of observational studies (14). The main criticism of these scales is that the summary scores involve inherent weighting of the component items. Instead of assigning a score for study quality, we chose to explore specific study quality items separately by performing meta-regression

Table 4. Results From Meta-Regression Analyses[a] of Weight Change and Risk of Colorectal Cancer for a Dose-Response Relationship (per 5 kg), 1997–2014

Covariate	No. of HRs	No. of Studies[b]	HR	95% CI	I^2, %	τ^2	Univariable			Multivariable		
							Ratio of HRs	95% CI	P Value	Ratio of HRs	95% CI	P Value
Model with no covariates	23	9	1.03	1.01, 1.05	41.6	0.001						
Cancer site												
Colorectal	13	7	1.04	1.02, 1.07	44.1	0.001	1.00	Referent		1.00	Referent	
Colon	2	2	1.04	0.98, 1.10			1.00	0.94, 1.06	0.892	1.02	0.95, 1.10	0.500
Rectal	8	4	1.02	0.98, 1.06			0.97	0.93, 1.02	0.267	0.98	0.94, 1.03	0.379
Sex												
Women	11	7	1.02	0.99, 1.04	30.1	<0.001	1.00	Referent		1.00	Referent	
Men	12	8	1.05	1.03, 1.08			1.03	1.00, 1.07	0.066	1.04	1.00, 1.08	0.061
Time frame for reporting body size change												
Early adulthood to midlife	16	6	1.03	1.01, 1.05	43.5	0.001	1.00	Referent		1.00	Referent	
Midlife to older age	7	3	1.06	0.98, 1.15			1.03	0.95, 1.12	0.507	1.05	0.91, 1.22	0.470
Method used to collect body size at each wave												
Measured at baseline and follow-up wave(s)	2	1	1.05	0.95, 1.16	44.0	0.001	1.00	Referent		1.00	Referent	
Measured at baseline, self-reported at follow-up wave(s)	10	3	1.07	1.01, 1.12			1.02	0.91, 1.13	0.761	1.08	0.89, 1.30	0.417
Self-reported at baseline and follow-up wave(s)	11	5	1.03	1.01, 1.05			0.98	0.89, 1.08	0.686	1.04	0.87, 1.25	0.611
Adjusted for physical activity												
No	7	3	1.05	1.00, 1.10	42.0	0.001	1.00	Referent		1.00	Referent	
Yes	16	6	1.03	1.01, 1.05			0.99	0.94, 1.04	0.533	0.98	0.91, 1.06	0.604
Proportion of baseline sample included in analysis, %[c]												
<80	10	3	1.04	1.01, 1.07	43.1	0.001	1.00	Referent		1.00	Referent	
≥80	9	5	1.03	1.00, 1.06			0.98	0.95, 1.03	0.437	0.97	0.93, 1.01	0.151

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Meta-regression models are fitted assuming random effects, which allows for a variance component τ^2 that accounts for the unexplained heterogeneity between studies. Note, when there is little heterogeneity across the studies, fixed-effect and random-effects meta-analyses will give similar estimates.

[b] The number of studies exceeds the total in the categories of sex and cancer site because some studies presented results for all the subgroups (e.g., for both men and women).

[c] The number of studies is 8; Hughes et al. (10) used a case-cohort design, and it was not appropriate to compare the proportion included in that analysis with those of the traditional cohort designs.
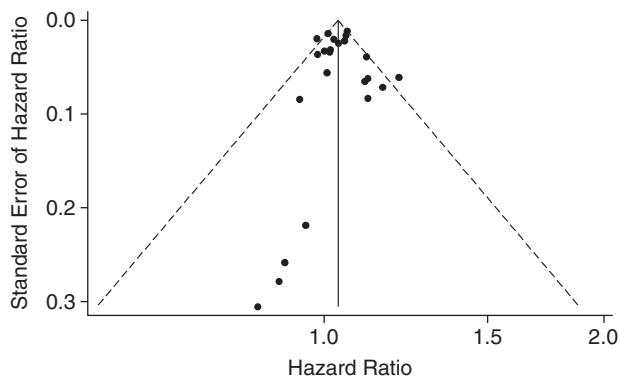
Figure 7. Funnel plot of the studies included in the meta-analysis comparing a dose-response relationship between weight gain and the risk of colorectal cancer, 1997–2014. The *x*-axis is on the log scale. Continuous line, no effect; dashed line, upper and lower 95% confidence limits.

analyses to see whether each item modified the pooled effect of change in weight on colorectal cancer (14).

Possible mechanisms

Several biological mechanisms have been postulated to explain the association between obesity and risk of colorectal cancer (34–37). The most studied pathways involve insulin, insulin-like growth factor-1 and insulin-like growth factor binding proteins, adipokines (e.g., leptin and adiponectin), and chronic inflammation (38, 39).

Conclusion

Obesity is an important risk factor for several solid cancers, including colorectal cancer, with a 33% increased risk of colorectal cancer for obese individuals compared with normal weight individuals (28). Weight gain and weight loss are important for public health policies and cancer prevention interventions, but few studies have assessed the effect of weight gain, and none have assessed changes in waist circumference with respect to the risk of colorectal cancer. In this meta-analysis, we found that the highest category of weight gain, measured by weight or body mass index, was positively associated with the risk of colorectal cancer when compared with a reference group of little or no weight gain. More studies are needed in order to elucidate whether there are different risks of colorectal cancer associated with weight gain or increasing abdominal fatness as measured by waist circumference.

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