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Title: Adult weight gain and colorectal adenomas – a systematic review and meta-analysis

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Abstract.

Background: Colorectal adenomas are known as precursors for the majority of colorectal carcinomas. While weight gain during adulthood has been identified as a risk factor for colorectal cancer, the association is less clear for colorectal adenomas. We conducted a systematic review and meta-analysis to quantify the evidence on this association.

Methods: We searched MEDLINE up to September 2016 to identify observational (prospective, cross-sectional and retrospective) studies on weight gain during adulthood and colorectal adenoma occurrence and recurrence. We conducted meta-analysis on high weight gain versus stable weight, linear and non-linear dose-response meta-analyses to analyze the association. Summary odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using a random effects model.

Results: For colorectal adenoma occurrence, the summary OR was 1.39 (95% CI: 1.17-1.65; I^2:43%, *N* =9 studies, cases=5,507) comparing high (midpoint: 17.4 kg) versus stable weight gain during adulthood and with each 5 kg weight gain the odds increased by 7% (2%-11%; I^2:65%, *N*=7 studies). Although there was indication of non-linearity ($P_{non\text{-}linearity}$ <0.001) there was an increased odds of colorectal adenoma throughout the whole range of weight gain. Three studies were identified investigating the association between weight gain and colorectal adenoma recurrence and data were limited to draw firm conclusions.

Conclusions: Even a small amount of adult weight gain was related to a higher odds of colorectal adenoma occurrence. Our findings add to the benefits of weight control in adulthood regarding colorectal adenomas occurrence, which might be relevant for early prevention of colorectal cancer.

Key words: Body weight gain, body weight change, colorectal adenomas, polyps, meta-analysis, observational studies

Key message: This is the first systematic review and meta-analysis summarizing evidence on adult body weight gain and colorectal adenomas. Per 5 kg body weight gain the odds of adenoma occurrence increased by 7% (2%-11%). These findings show the benefits of weight control from early adulthood regarding the occurrence of colorectal adenomas, which might be relevant for early colorectal cancer prevention.

Introduction.

In 2012, colorectal cancer was the third most common cancer in men and the second in women, and about 694,000 deaths from colorectal cancer were documented worldwide.[1] Many modifiable lifestyle factors, including smoking, dietary factors, physical activity as well as obesity and weight gain during adulthood have been identified as influencing factors for risk of colorectal cancer.[2, 3] There is consent that adenomas –non-cancerous tumors– in the colon or rectum are precursors to development of colorectal cancer, known as the adenoma-to-carcinoma sequence.[4, 5] Regarding this aspect, it is likely that the same risk factors as for colorectal cancer are involved in the etiology of colorectal adenomas. A growing body of evidence suggest that smoking,[6] physical activity,[7] dietary intake of fiber,[8] meat,[9] and alcohol,[10] are also associated with risk of colorectal adenomas, and serrated adenomas,[11] a subtype with strong malignant potential.[12] In addition, body fatness –both general and abdominal– has been linked to increased risk of colorectal adenomas.[13-16] A recent meta-analysis indicated that the visceral adipose tissue, related to metabolic adverse effects is associated with advanced colorectal adenomas and might be a mediator for the association between obesity and colorectal adenomas.[17] Moreover, adult weight gain, a marker of body fat mass fluctuation, is related to metabolic alterations as well, even within the normal body weight range and already during early adulthood.[18] [19] In this context, beyond body fatness, epidemiological studies have investigated whether adult weight gain is related to the occurrence and recurrence of colorectal adenomas. Even though most studies indicated a positive association between adult weight gain and risk of colorectal adenomas, some of these findings still allowed for the possibility of no increase in risk and uncertainty remains in the exact magnitude of any association.[20-29]. So

far, no systematic review or meta-analysis has been conducted that summarize findings on this association.

Thus, to quantify this association we conducted a meta-analysis of epidemiological studies (including cross-sectional, case-control and prospective studies) on adult weight gain and colorectal adenomas and recurrence. In addition, we explored linear and non-linear dose-response relations on adult weight change and the occurrence of colorectal adenomas. And finally, we investigated if study design, sex, adenoma location (colon vs. rectum), time period of weight assessment (weight gain in early adulthood vs during middle age), and adjustment for general body fatness might influence the association between adult weight gain and colorectal adenoma occurrence.

Materials and Methods.

This report was conducted according to standard criteria provided by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.[30]

Literature Search

The literature search has been conducted as part of the World Cancer Research Fund International Continuous Update Project/ American Institute for Cancer Research Continuous Update Project following a predefined protocol (http://www.wcrf.org/sites/default/files/protocol_colorectal_cancer.pdf). Relevant studies on weight gain during adulthood and colorectal adenomas were identified by searching PubMed up to December 2015. Initially (up to December 2005), several other databases were used, including Embase, CAB Abstracts, ISI Web of Science, BIOSIS, LILACS, Cochrane library, CINAHL, AMED, National Research Register and In Process Medline. As all the relevant studies were

identified using PubMed, a change in the protocol was made and only PubMed was used for the updated searches. The literature search included two outcomes, colorectal cancer and colorectal adenomas. As this systematic review and meta-analysis focus on colorectal adenomas only, we excluded studies on colorectal cancer. We conducted an update of the literature search in Medline (PubMed) for articles on adult weight change and colorectal adenomas until September 2016.

Study selection

Studies were selected if they 1) reported on the association between adult weight change and adenoma occurrence or recurrence, 2) used a cohort, nested case-control, case-cohort, case-control, cross-sectional design, or follow-up studies of randomized clinical trials, and 3) provided effect estimates for this association (including hazard ratio or odds ratio (OR)) with the 95% confidence interval (95% CIs). For simplicity, we use the term OR for all these estimates in the present manuscript. In addition, we defined studies as prospective if a follow-up period between second weight assessment and diagnosis of colorectal adenomas was available and as retrospective if the second weight measure was taken at time of colorectal adenoma assessment or recalled 1 year before. We focused on two different outcomes: adenoma occurrence (no previous adenoma was known) and adenoma recurrence (prior adenoma was diagnosed). Studies not published as original articles were excluded. Furthermore, we excluded one study reporting on changes of BMI instead of weight change because a conversion into weight change was not possible.[31]

Data extraction

The following information was extracted from each study: last name of the first author, publication year, country of origin, underlying study source, duration of follow-up (if applicable), sex, age (range or mean), outcome (occurrence or recurrence), outcome assessment, sample size, number of cases, number of controls (if applicable), assessment of weight change and age at weight assessment, quantity of weight change, most fully adjusted estimates and corresponding 95% CIs, and variables adjusted for in the statistical analysis. Data for men and women, or colon and rectal adenomas, were extracted separately, if information was provided by the single studies.

Statistical analysis

The associations between weight gain during adulthood and colorectal adenoma occurrence or recurrence were analyzed by comparing extreme categories of weight gain during adulthood (high weight gain vs. low weight gain), and summary ORs (95% CI) were calculated by applying random effects models. Two studies reported on adult weight gain in pounds,[24, 26] and quantifications were converted in kg (1 kg ≅ 2.2 lbs). For one study, we converted adult weight change in kg/year into weight change per kg by multiplying the quantification with the time interval between both weight assessments.[28] If stable weight was not used as reference category in single studies,[21, 23] we used the method of Hamling *et al*. to convert risk estimates to being relative to this reference category.[32] For studies that reported estimates stratified by sex,[22] or adenoma site (colon, rectal and both),[29] a fixed effect model was used to combine the estimates for the main analysis.

Heterogeneity between studies was investigated by using the I^2 test and to investigate potential influencing factors for the association between adult weight gain and colorectal

adenoma occurrence, we performed subgroup and meta-regression analyses.[33] We stratified our analysis by: study design (prospective vs. retrospective), sex (men vs. women), site of adenoma (colon vs. rectum), time of weight assessment (early vs. mid-life adulthood), definition of high weight gain category (≥10 vs <10 kg), used reference category (weight loss included vs. stable weight), outcome assessment (colonoscopy vs. sigmoidoscopy vs. self-repots), geographic area (Asia vs. Europe vs. USA), indication (without indication vs. with indication), and adjustment (yes vs. no) for baseline weight/body mass index/waist circumference, physical activity, smoking, alcohol intake, and family history of colorectal cancer. Stratified analyses for adenoma recurrence were not conducted because of the restricted number of studies.

Furthermore, we performed a linear dose-response meta-analysis of the association between adult weight gain per 5 kg and colorectal adenoma occurrence. Study-specific slopes (linear trends) and 95% CIs from the natural logarithm of the ORs across categories of weight change were calculated by using the method described by Greenland and Longnecker and implemented by Orsini.[34, 35] This method requires the distribution of cases, person-years/non-cases, the quantification of the exposure and the risk estimates with corresponding 95% CIs for at least three weight change categories. The distribution of cases, person years or non-cases was estimated if the information was missing. The mid-point between the lower and upper limit for each exposure category was calculated, if studies reported ranges and mean values were not reported. When the lowest or highest category was open-ended, we expected that the range was similar to the adjacent category. Some of the studies included weight loss in the reference category, and we excluded these studies in a sensitivity analysis.[20, 25, 27] In another sensitivity analysis, we repeated the doe-response meta-analysis stratified by study design. In

addition, we investigated adult weight gain per kg/year to consider different time periods between the both weight assessments.

Moreover, a potential non-linear relation between weight change during adulthood and colorectal adenoma occurrence was investigated by performing cubic spline regression models and indication of non-linearity was tested by using likelihood ratio test.[36] We included all categories of weight change (even the weight loss categories) to get an idea about the whole relation between weight change and occurrence of colorectal adenoma. We repeated the non-linear dose-response meta-analysis only including prospective studies. For adenoma recurrence the number of studies was restricted and we were not able to investigate the dose-response relation.

Small study effects such as publication bias were assessed by visual inspection of the funnel plot for asymmetry and by applying Egger's test.[37]

All statistical analyses were performed using STATA version 13.1 software (StataCorp, College Station, TX).

Results.

The flow chart of the literature search is shown in **Figure 1**. In total, we included 10 studies (6 retrospective and 4 prospective studies)[20-29] on adult weight change and colorectal adenomas in our meta-analysis, with 9 studies focusing on occurrence[20-23, 25-29] and 3 studies on recurrence.[22-24] The characteristics of included studies are shown in **Table 1**.

Adenoma Occurrence

The association between weight gain during adulthood and colorectal adenoma occurrence was investigated in 9 studies (5 retrospective and 4 prospective studies),[20-23, 25-29] including 5,507 cases among 59,187 participants. Out of these, weight gain was assessed during early adulthood in 6 and during mid-life in 3 studies.

In the meta-analysis comparing high (midpoint 17.4 kg) versus low weight gain during adulthood, the summary OR for colorectal adenoma occurrence was 1.39 (95% CI: 1.17-1.65) with moderate heterogeneity (I^2: 43%, $P_{heterogeneity}$=0.08) (**Figure 2**).

Subgroup analyses are shown in **Table 2**. The findings stratified by sex suggested that the association was stronger in women [summary OR (95% CI) 1.36 (1.01-1.83); *N* =4 studies] compared to men [summary OR (95% CI) 1.05 (0.71-1.55); *N* =3 studies], but differences were not statistically significant (*P* for heterogeneity by sex=0.51). When we restricted the stratified analysis by sex to studies providing both information (for men and women separately, *N* = 2 studies), the summary OR for women was 0.78 (95% CI: 0.31-1.95) and for men 1.15 (95% CI: 0.46-2.86), with no indication for interaction (*P* for heterogeneity by sex=0.68). Stronger associations were observed for studies which defined high adult weight gain as greater or equal than 10 kg [summary OR (95% CI) 1.55 (1.26-1.90)] compared to studies investigating less than 10 kg [summary OR (95% CI) 1.24 (0.95-1.63)]; but differences were not statically significant (*P* for heterogeneity by weight gain category=0.21). We did not observe a difference of the association after stratification by study design (prospective vs. retrospective studies) (**Table 2** and **Supplementary figure S1**) and adjustment for excess body weight (**Table 2**).

In other subgroup analyses (stratification by site of adenoma, time of weight assessment, geographic area, indication and study quality criteria, such as definition of reference category,

outcome assessment, adjustment for confounders) the findings remained robust and no statistically significant differences were observed.

For the dose-response meta-analysis we included 7 studies.[20, 21, 23, 25, 27-29] Per each 5 kg weight gain during adulthood the odds of colorectal adenoma was increased by 7% (95% CI: 2%-11%) (**Figure 3**). There was moderate to high heterogeneity (I^2: 65%, $P_{heterogeneity}$=0.009), In a sensitivity analysis, excluding studies using a combination of adult weight gain and weight loss in the reference category,[23, 28, 29, 38] the odds of colorectal adenoma was slightly higher [summary OR (95% CI) per 5 kg weight gain during adulthood: 1.08 (1.03-1.12), N=4 studies)] and there was no indication for heterogeneity between the studies (I^2: 0%, $P_{heterogeneity}$=0.87). No differences by study design (prospective vs retrospective) was observed (**Supplementary figure S2).** The non-linear dose-response curve indicated evidence of non-linearity ($P_{non\text{-}linearity}$<0.001), but no threshold of adult weight gain in relation to risk increase was observed. The curve shows an increase odds of colorectal adenoma throughout all the range of adult weight gain investigated, although the curve was steeper at lower levels of weight gain than at higher levels (**Figure 4**). After restricting our non-linear dose-response meta-analysis to prospective studies only, findings did not change substantially (**Supplementary figure S3).** When we considered the time interval of weight gain during adulthood, the odds of colorectal adenoma was 30 % increased by each kg adult weight gain per year [summary OR (95% CI) for 1 kg/y: 1.30 (1.10-1.55); I^2: 70%, $P_{heterogeneity}$=0.003].

There was no indication for publication bias (Egger's test: P=0.57; **Supplementary figure S4)**

Adenoma Recurrence

For the analysis on weight gain during adulthood and adenoma recurrence we included 3 studies (2 retrospective and 1 prospective studies),[22-24] including 1,350 cases among 5,559 participants. One study reported on weight gain during early adulthood and 2 on weight gain during mid-life. The summary OR (95% CI) in high versus low meta-analysis was 1.14 (0.88-1.49), without statistically significant indication of heterogeneity between studies (I^2=48%, $P_{heterogeneity}$=0.15) (**Figure 2**). We did not conduct subgroup analyses, linear and non-linear dose-response meta-analysis of weight gain and adenoma recurrence because of the limited number of studies.

Discussion.

This is the first systematic review and meta-analysis reporting on the association between weight gain during adulthood and colorectal adenomas. Findings indicated that high adult weight gain was associated with higher odds of adenoma occurrence. For a 5 kg weight gain during adulthood the odds of colorectal adenoma occurrence increased by 7%. Although there was indication for a non-linear relation, with a slightly steeper relation at lower than higher values of weight gain, the curve shows an increased odds of colorectal adenomas throughout all the range of adult weight gain investigated and a reduction in odds of adenoma occurrence with weight loss. For adenoma recurrence the number of studies was too limited to draw clear conclusions.

Our findings on adult weight gain during adulthood and colorectal adenoma occurrence are comparable with findings on weight gain and risk of colorectal cancer.[3] Our findings indicated that for each 5 kg gain in weight during adulthood the odds of colorectal adenoma increased by 7% (2%-11%), and the risk for colorectal cancer by 4% (2%-5%).[3] In addition, these findings are in line with previous reports on anthropometric measures, including measures

of general and abdominal obesity as well as quantification of specific fat depots, showing positive associations between body fatness and colorectal adenomas.[13-17, 39]

We did not identify statistically significant differences in subgroups analyses, but findings need more consideration. After stratification by sex, findings indicated that the association was restricted to women and not significant in men, however, the low number of studies in these subgroup analyses is a limitation. To explore if these findings might be influenced by other characteristics of the studies, we restricted this analysis only to studies that provided findings for both, men and women separately.[22, 23] These two studies, one conducted in Korea, including participants undergoing a screening program, and the other study from the Netherlands, including participants with MMR gene mutation carrier, indicated that associations were stronger in men than in women, but differences were not statistically significant.[22, 23] The meta-analysis on weight gain during adulthood and risk of colorectal cancer provided evidence that the association was stronger in men than in women,[3] whereas findings on anthropometric measures and colorectal adenoma did not show differences between men and women.[13, 15-17] However, for colorectal adenoma the number of studies accounting for men and women separately is limited and studies focusing on differences are warranted. After stratification by site, we did not observe statistically significant differences between colon and rectal adenomas with weight gain during adulthood, which is comparable to previous findings on colorectal cancer.[3] But again, number of studies were limited and further studies are needed. We stratified our analysis by studies adjusting and not adjusting for body fatness defined by weight, BMI, or waist circumference. The results did not differ appreciably between the two groups, indicating that weight gain during adulthood is associated with colorectal adenoma, independently of body fatness.

The underlying mechanism for the association between adult weight change and adenoma occurrence is not clear yet. Lifestyle intervention studies provided evidence that weight loss improved levels of oxidative stress (including CRP, oxidized low-density lipoprotein, fluorescent oxidation products, F2-isoprostanes), metabolic biomarkers (including leptin and adiponectin) and insulin resistance,[40-43] whereas observational studies indicated that body weight gain during adulthood is related with metabolic alterations.[18, 19, 44] Recently, a large European cohort study reported that individuals with normal weight but a metabolic unhealthy status (defined by hyperinsulinaemia) were at higher risk of colorectal cancer compared to metabolic healthy and normal weight individuals.[45] This study also showed that overweight individuals, but metabolically healthy were at lower risk of colorectal cancer compared to overweight individuals who were metabolic unhealthy. These findings underline the hypothesis that metabolic alterations beyond BMI might play a role in the etiology of colorectal cancer. While metabolic perturbations are associated with increased risk of colorectal cancer,[38, 45-48] the evidence for colorectal adenomas is less clear,[49-52] explainable by the lack of studies, particularly prospective studies.[53] Findings from case-control and cross-sectional studies indicated that the prevalence of the metabolic syndrome and insulin resistance was higher and levels of adiponectin lower in individuals with colorectal adenoma compared to the control goup,[52, 54, 55] which might be a potential explanation for our observed association. More studies investigating the pathomechanisms of colorectal adenomas in relation with adult weight gain and body fatness in general, are needed.

Our meta-analysis has several strengths. First, to our knowledge this is the first systematic review and meta-analysis summarizing the evidence between body weight gain during adulthood and colorectal adenoma. Second, this report does not focus on high versus low

analysis only, but linear and non-linear dose-response analysis were conducted to explore the strength and shape of the relation between adult weight gain and colorectal adenoma occurrence. Third, we performed stratified analysis to investigate the robustness of our findings, considering biological and methodological factors. In this context, we could show that the association persisted even after adjusting for body fatness, defined by weight, BMI, or waist circumference. On the contrary, our study has limitations that should be discussed. First our study included both, retrospective and prospective studies. However, we stratified our meta-analysis by study design and findings were comparable. In addition, most of the studies included asymptomatic individuals and only two studies were based on individuals with indications. In our stratified analyses results did not change considerably, making recall bias from case-control or cross-sectional studies less likely. Second, some of the studies included in our meta-analysis relied on colorectal adenoma detection rather than onset and it is possible that adenomas have developed earlier. If studies did not conduct a colonoscopy at baseline for cohort studies or in the past for case-control and cross-sectional studies, prevalent colorectal adenomas are likely included, which might have an influence on the temporal sequence of the relation between adult weight change and colorectal adenoma occurrence. However, as discussed earlier colorectal adenomas mostly do not show any symptoms and it is unlikely that participants changed their weight intentionally. In addition, a previous meta-analysis showed that unintentional weight loss was less than 10% for individuals diagnosed with colorectal adenomas.[56] Third, measurement error of adult weight gain cannot be ruled out. For early weight gain information was based on recalled weight, which might be a valid measurement,[57, 58] but tended to be underreported depending on the current weight and amount of weight gain.[59] If body weight was underestimated in the studies included in our meta-analysis, estimates would be biased toward

the null. Fourth, the analysis on adenoma recurrence and subgroup analyses by sex and adenoma site were restricted by the small number of studies providing the information separately. These findings should be interpreted with caution and more studies investigating sex- and site-specific associations between adult weight gain and colorectal adenoma occurrence and recurrence are warranted.

In conclusion, this meta-analysis indicated evidence that weight change during adulthood is associated with colorectal adenoma occurrence independently of excess body weight. In the non-linear dose-response meta-analysis, colorectal adenomas were less common in individuals reporting weight loss and more common in individuals with weight gain. Even a small amount of adult weight gain was related to higher odds of colorectal adenoma. Our findings show the benefits of weight control from early adulthood regarding the occurrence of colorectal adenomas – a known precursor of colorectal cancer – which might be relevant for early prevention.

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Disclosures: The authors have declared no conflicts of interest.

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Figure Legends.

Figure 1: Flow chart of study selection

Figure 2: High vs low meta-analysis for weight gain and colorectal adenoma occurrence and recurrence

Figure 3: Dose-response meta-analysis for weight gain per 5 kg and colorectal adenoma occurrence

Figure 4: Non-linear dose-response meta-analysis for weight gain and colorectal adenoma occurrence ($P_{non\text{-}linearity}$ <0.001)

Figure 1

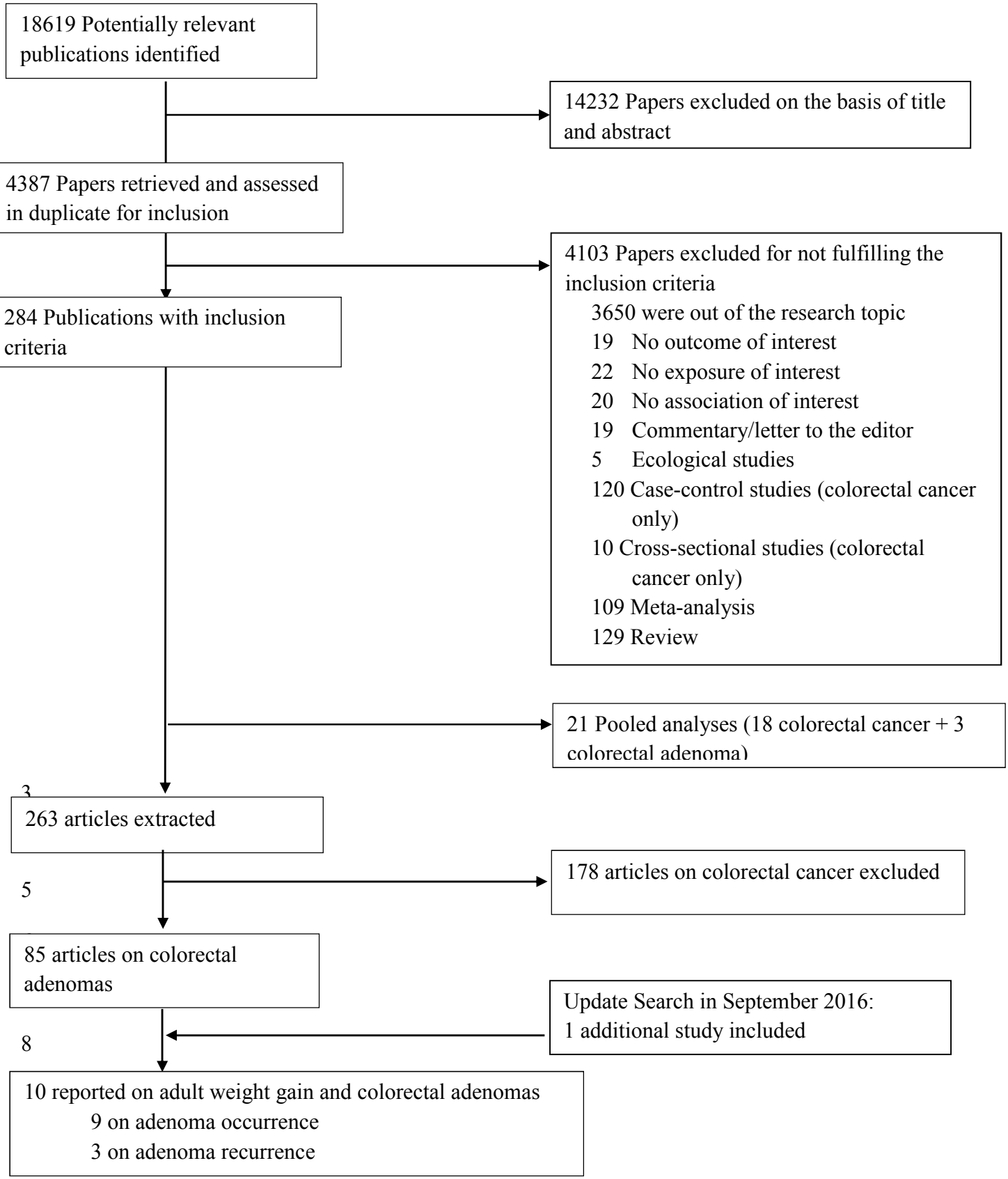

18619 Potentially relevant publications identified
14232 Papers excluded on the basis of title and abstract
4387 Papers retrieved and assessed in duplicate for inclusion
4103 Papers excluded for not fulfilling the inclusion criteria
3650 were out of the research topic
19 No outcome of interest
22 No exposure of interest
20 No association of interest
19 Commentary/letter to the editor
5 Ecological studies
120 Case-control studies (colorectal cancer only)
10 Cross-sectional studies (colorectal cancer only)
109 Meta-analysis
129 Review
284 Publications with inclusion criteria
21 Pooled analyses (18 colorectal cancer + 3 colorectal adenoma)
263 articles extracted
178 articles on colorectal cancer excluded
85 articles on colorectal adenomas
Update Search in September 2016:
1 additional study included
10 reported on adult weight gain and colorectal adenomas
9 on adenoma occurrence
3 on adenoma recurrence

Figure 2

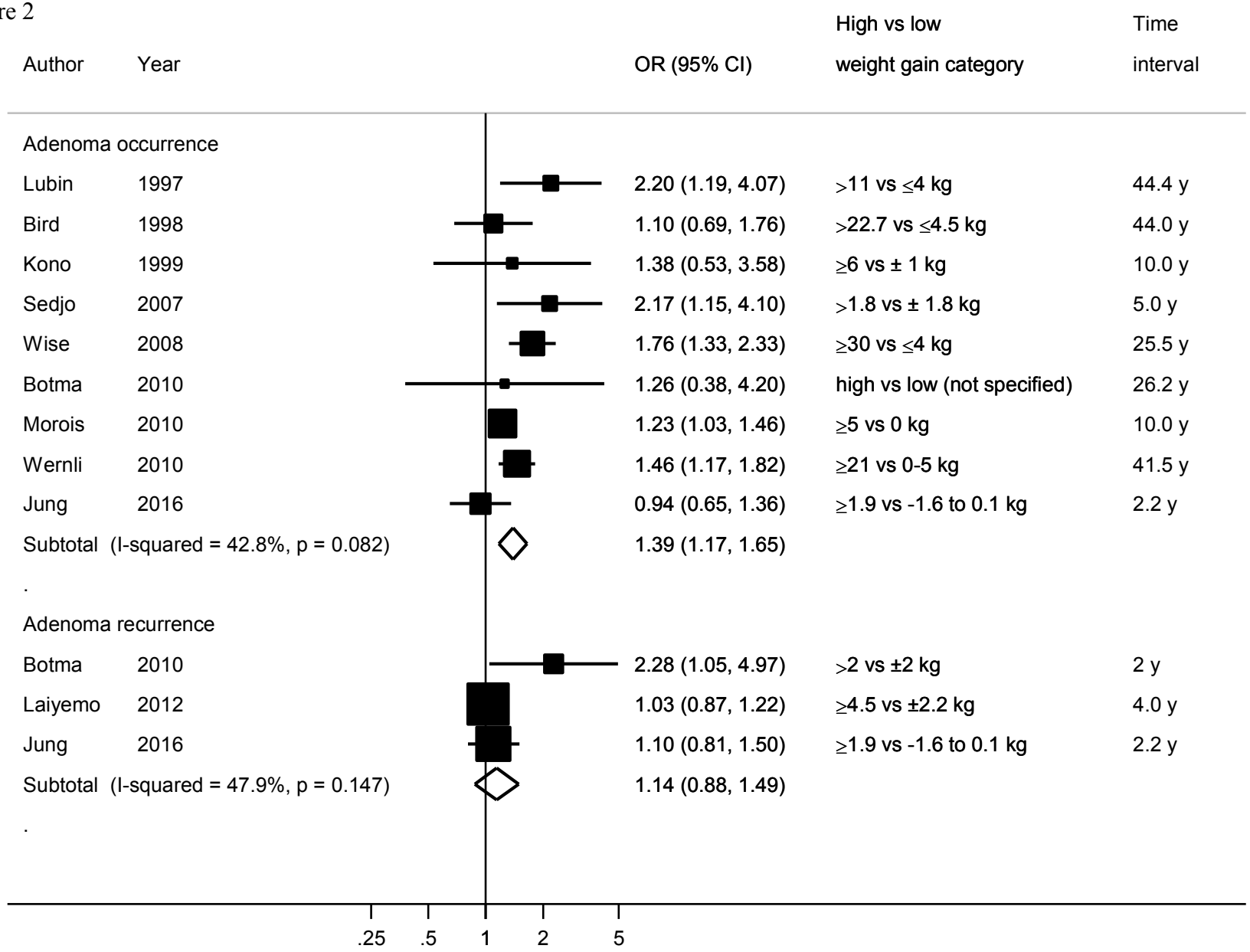

Author
Year
OR (95% CI)
High vs low weight gain category
Time interval
Adenoma occurrence
Lubin 1997 2.20 (1.19, 4.07) >11 vs ≤4 kg 44.4 y
Bird 1998 1.10 (0.69, 1.76) >22.7 vs ≤4.5 kg 44.0 y
Kono 1999 1.38 (0.53, 3.58) ≥6 vs ± 1 kg 10.0 y
Sedjo 2007 2.17 (1.15, 4.10) >1.8 vs ± 1.8 kg 5.0 y
Wise 2008 1.76 (1.33, 2.33) ≥30 vs ≤4 kg 25.5 y
Botma 2010 1.26 (0.38, 4.20) high vs low (not specified) 26.2 y
Morois 2010 1.23 (1.03, 1.46) ≥5 vs 0 kg 10.0 y
Wernli 2010 1.46 (1.17, 1.82) ≥21 vs 0-5 kg 41.5 y
Jung 2016 0.94 (0.65, 1.36) ≥1.9 vs -1.6 to 0.1 kg 2.2 y
Subtotal (I-squared = 42.8%, p = 0.082) 1.39 (1.17, 1.65)
Adenoma recurrence
Botma 2010 2.28 (1.05, 4.97) >2 vs ±2 kg 2 y
Laiyemo 2012 1.03 (0.87, 1.22) ≥4.5 vs ±2.2 kg 4.0 y
Jung 2016 1.10 (0.81, 1.50) ≥1.9 vs -1.6 to 0.1 kg 2.2 y
Subtotal (I-squared = 47.9%, p = 0.147) 1.14 (0.88, 1.49)
.25
.5
1
2
5

Figure 3

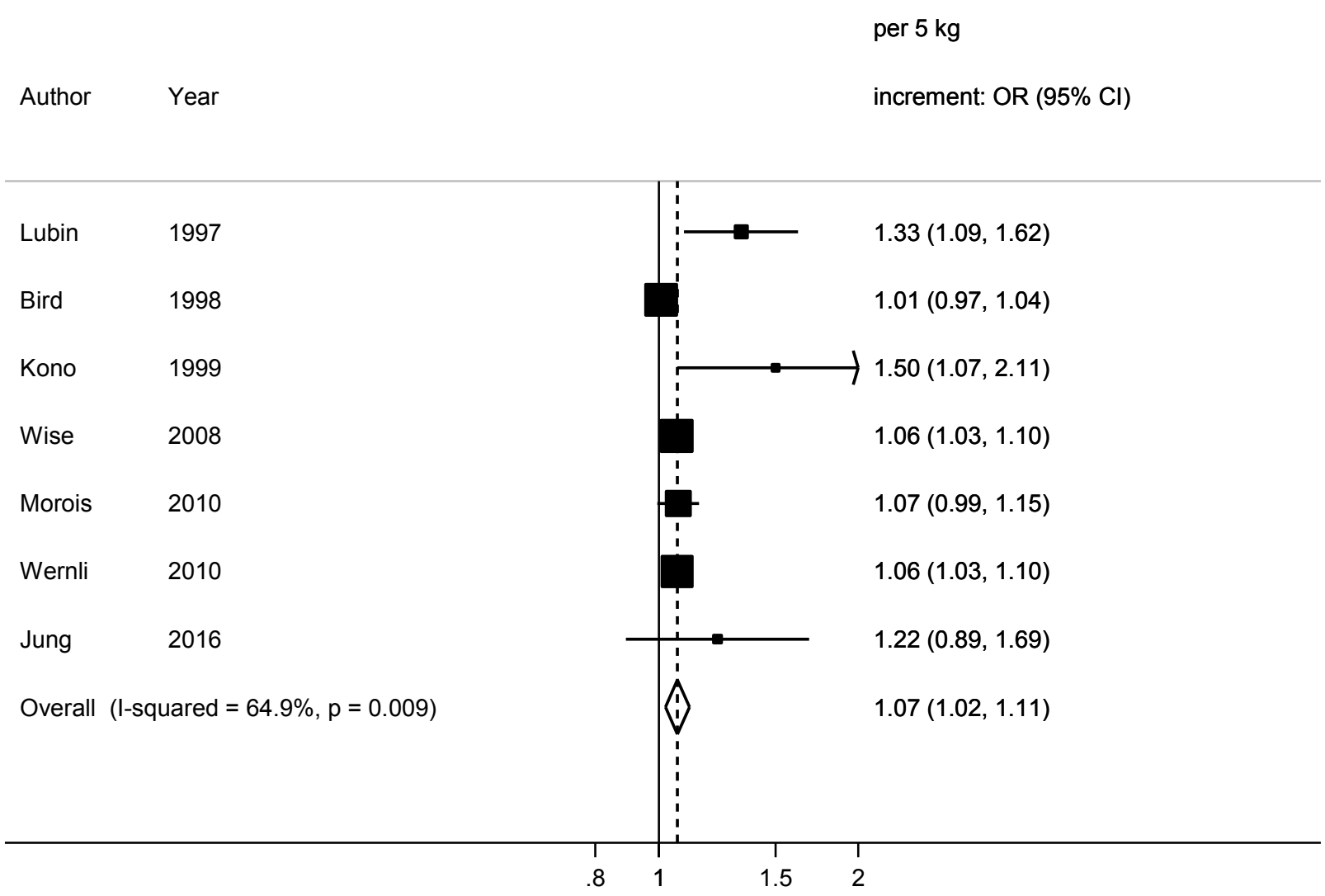

per 5 kg
Author
Year
increment: OR (95% CI)
Lubin 1997 1.33 (1.09, 1.62)
Bird 1998 1.01 (0.97, 1.04)
Kono 1999 1.50 (1.07, 2.11)
Wise 2008 1.06 (1.03, 1.10)
Morois 2010 1.07 (0.99, 1.15)
Wernli 2010 1.06 (1.03, 1.10)
Jung 2016 1.22 (0.89, 1.69)
Overall (I-squared = 64.9%, p = 0.009) 1.07 (1.02, 1.11)
.8
1
1.5
2

Figure 4.

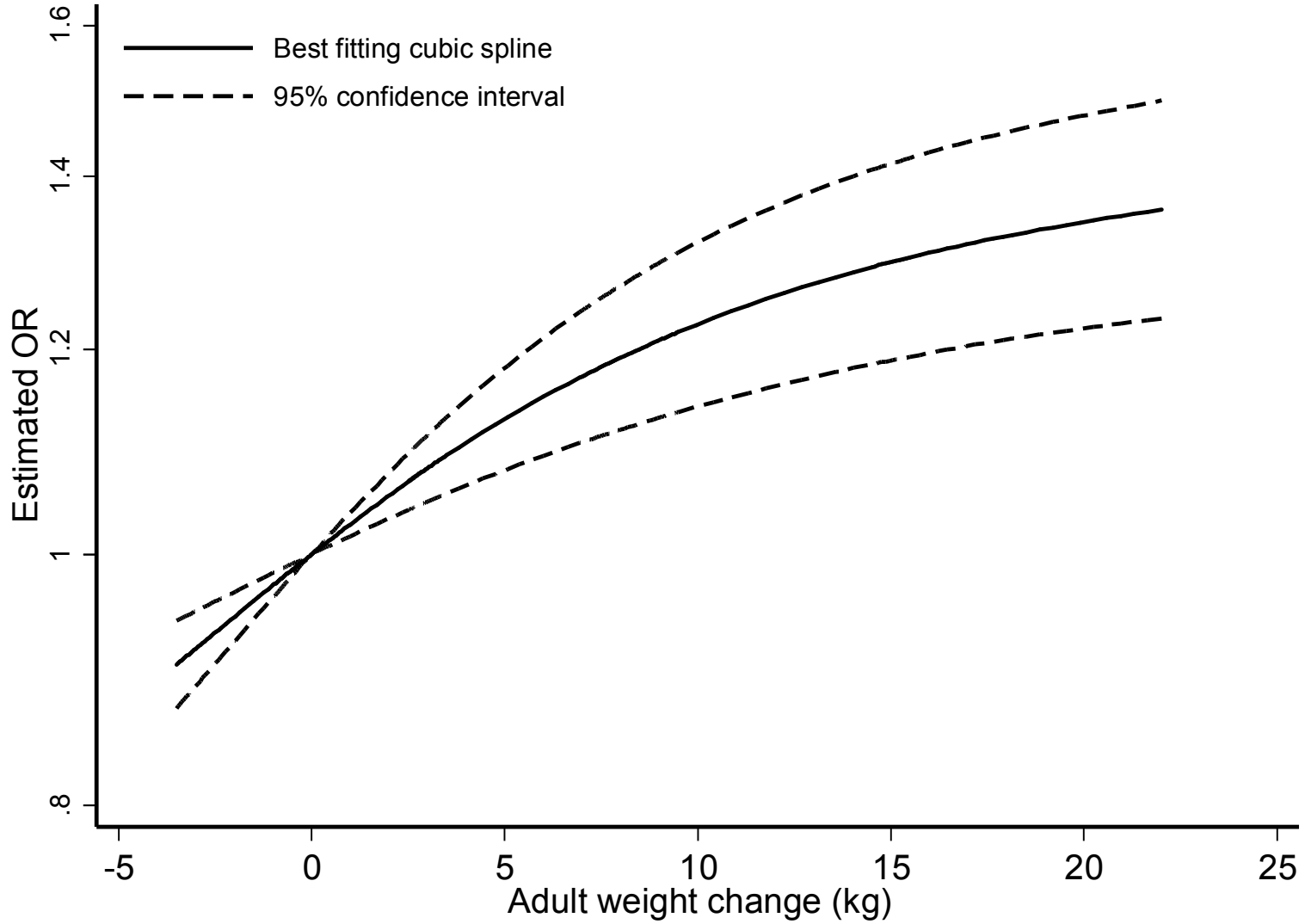

Best fitting cubic spline
95% confidence interval
Estimated OR
.8
1
1.2
1.4
1.6
-5
0
5
10
15
20
25
Adult weight change (kg)

Table 1. Characteristics of the included studies

Author, year (country)	Study source, study design, (follow-up)	Sex, Age	Outcome, Outcome assessment	Sample size, *N* cases, controls	Exposure assessment	Exposure categories	Relative Risk (95% CI)	Adjustment
Retrospective studies								
Lubin 1997 (Israel)[25]	Screening Program of the gastroenterology Department at the Tel Aviv Medical Center, Retrospective study	M & F, 21-75 y	colorectal adenomas, colonoscopy	cases: 196 controls: 196	self-reported baseline weight and recalled weight at age 18	<4 kg (ref), 4-11 kg, >11 kg	**<4**: 1 **4-11**: 1.5 (1.1-2.1) **>11**: 2.2 (1.2-4.1)	total energy and physical activity
Bird, 1997 (US)[20]	Screening at Southern California Kaiser Permanente medical centers, Retrospective study	M & F, 50-75 y	colorectal adenomas, sigmoidoscopy	cases: 483 controls: 483	self-reported baseline weight and recalled weight at age 18	Quartiles: Q1:-34.1-4.5 kg (ref) Q2:>4.5-13.6 kg Q3:>13.6-22.7 kg Q4:>22.7-81.8 kg	**Q1**: 1 **Q2:** 1.0 (0.7-1.5) **Q3:** 1.1 (0.7-1.7) **Q4:** 1.1 (0.7-1.8)	sex, age, date sigmoidoscopy, center, BMI
Kono, 1999 (Japan)[21]	Health examination at the Japan Self Defence Forces, Retrospective study	M, 47-55 y	colon adenomas, colonoscopy	cases: 189 controls: 226	measured baseline weight and recorded weight 10 y before	≤ -2 kg (ref) -1-1kg 2-5 kg ≥ 6kg	**≤ -2:** 1 **-1-1:** 1.6 (0.9-2.7) **2-5:** 1.8 (1.0-3.0) **≥ 6**: 2.2 (1.0-4.8)	hospital, rank in the self-defence force, smoking, alcohol use
Wernli, 2010 (US)[29]	Group Health, Retrospective study	M & F, 20-74 y	colorectal adenomas, colonoscopy	colon: 519 rectum: 691 both: 227 controls: 772	self-reported recalled weight 1y before colonoscopy and at age 18 y	weight loss 0-5 kg 6-10 kg 11-20 kg >21 kg	**Colon**: **weight loss**: 1.03 (0.60-1.78) **0-5 kg**: 1 **6-10 kg**: 1.23 (0.83-1.82) **11-20 kg**: 1.18 (0.84-1.66) **>21 kg**: 1.41 (0.99-2.02) **Rectum**: weight loss: 1.26 (0.78-2.03) 0-5 kg: 1 6-10 kg: 1.37 (0.96-1.96) 11-20 kg: 1.28 (0.94-1.75) >21 kg: 1.29 (0.93-1.80) **Both lesions:** weight loss: 1.22 (0.54-2.74) 0-5 kg: 1 6-10 kg: 1.34 (0.74-2.44) 11-20 kg: 1.90 (1.15-3.14)	age, sex, race, education, smoking status, alcohol intake, NSAID use, family history of CRC, menopausal status, hormone use

							>21 kg: 2.16 (1.28-3.63)	
Laiyemo, 2012 (US)[24]	Polyp Prevention Trial, Retrospective study, 4 y	M & F, 61.0 y	colorectal adenoma recurrence, colonoscopy	*N*: 1,826 Recurrence: 723	measured weight at baseline and after 4 y (at diagnosis of recurrence)	loss ≥ 10 ibs loss (5-9 ibs) no change (ref) 5-9 ibs ≥10 ibs	**≤-**10 ibs: 0.91 (0.77-1.07) -5- -9 ibs) 0.90 (0.76-1.07) **no change**: 1 (ref) 5-9 ibs: 0.97 (0.82-1.16) ≥10 ibs: 1.03 (0.87-1.23)	age, sex, NSAID use, smoking status, baseline weight, dietary randomized assignment, family history of CRC
Jung, 2016 (Korea)[23]	Health screening program at Kangbuk Samsung Hospital, Retrospective study, 2.2 y	M & F, 41.2 y	colorectal adenomas and recurrence, colonoscopy	*N*: 3,121 without and 2,176 with adenoma Cases: 447 Recurrence: 591	measured weight at baseline and after 2.2 y (at diagnosis of adenoma or recurrence)	Quartiles: Q1:<-1.6 kg (ref) Q2-1.6-0.1 kg Q3:0.2-1.8 kg Q4:≥ 1.9 kg	**<u>Adenomas:</u>** **All:** **Q1**: 1 **Q2:** 1.24 (0.95-1.63) **Q3:** 1.28 (0.98-1.66) **Q4:** 1.17 (0.89-1.53) **Men:** **Q1**: 1 **Q2:** 1.31 (0.98-1.74) **Q3:** 1.31 (0.98-1.74) **Q4:** 1.25 (0.94-1.67) **Women:** **Q1**: 1 **Q2:** 0.84 (0.38-1.88) **Q3:** 1.11 (0.53-2.31) **Q4:** 0.62 (0.25-1.51) **<u>Recurrence:</u>** **All:** **Q1**: 1 **Q2:** 1.17 (0.93-1.47) **Q3:** 1.25 (0.98-1.58) **Q4:** 1.29 (1.02-1.64) **Men:** **Q1**: 1 **Q2:** 1.15 (0.91-1.46) **Q3:** 1.28 (1.00-1.64) **Q4:** 1.31 (1.03-1.67) **Women:** **Q1**: 1 **Q2:** 1.23 (0.51-2.99) **Q3:** 1.20 (0.46-3.17) **Q4:** 1.23 (0.45-3.36)	Age, sex, smoking status, family history of CRC, NSAID use, baseline weight

Prospective studies

Sedjo, 2007 (US)[26]	Insulin Resistance Atherosclerosis Study, Prospective study, ~5y	M & F, mean age 64 y	colorectal adenomas, colonoscopy	*N*: 600 cases: 136	measured baseline weight and prospective weight after 5 y	≤ -4 pounds -4-4 pounds (ref) >4 pounds	**≤-4**: 1.52 (0.60-3.87) **4-4**: 1 **>4**: 2.17 (1.15-4.11)	age, sex, clinic, ethnicity, smoking, estimated energy expenditure, previous polyp history, baseline BMI
Wise, 2008 (US)[27]	Black Women's Health Study Prospective study, 6.3 y	F, mean 43.5 y	colorectal adenomas , self-reported	*N*: 33,403 Cases: 1,189	self-reported baseline weight and recalled weight at age 18	<5 kg (ref), 5-14 kg 15-29 kg ≥30 kg	<5 kg: 1 5-14 kg: 1.44 (1.09-1.91) 15-29 kg: 1.57 (1.20-2.06) ≥30 kg: 1.76 (1.33-2.33)	Age, questionnaire cycle, physical activity, family history of colorectal cancer, smoking, education, nonsteroidal anti-inflammatory drug use, menopausal status, postmeno-pausal hormone use, red meat intake, fiber intake, energy, BMI at age 18
Botma, 2010 (The Netherlands)[22]	GEOLynch study (MMR gene mutation carrier), Prospective study, 1.7 y	M & F, 44.2 y	colorectal adenomas and recurrence, colonoscopy	*N*: 243 Cases: 22 Recurrence: 36	self-reported baseline weight and recalled weight at age 18 (for occurrence), and after 2 y (for recurrence)	For occurrence: grouped by median (not specified), for recurrence: ± 2 kg >2 kg	**Adenomas:** **Men:** low 3.60 (0.38-34.28) **Women:** 0.83 (0.20-3.48) **Recurrence:** **Men:** ± 2 kg: 1 >2 kg: 1.73 (0.67-4.45) **Women:** ± 2 kg: 1 >2 kg: 4.09 (1.04-16.19)	age, sex, smoking status, alcohol intake

Morois, 2010 (France)[28]	E3N-EPIC-study – France, Prospective study, 2 y	F, mean 53.1 y	Colon and rectum adenomas, colonoscopy	*N*: 17,391 cases: 1,408	self-reported weight at baseline and self-reported prospective weight every 2 y	<0 kg/year 0 (ref) kg/year 0.1-0.49 kg/year ≥ 0.5 kg/year	<0: 1.12 (0.92-1.35) 0 (ref) 0.1-0.49: 1.25 (1.05-1.49) ≥ 0.5: 1.23 (1.03-1.46)	energy intake, alcohol intake, total physical activity, smoking status, CRC in first degree relatives, educational level, menopausal status, use of menopausal hormone therapy

BMI, body mass index; CRC, colorectal cancer, F, female; M, male; NSAID, non-steroidal anti-inflammatory drugs; *N*, number; Y, year

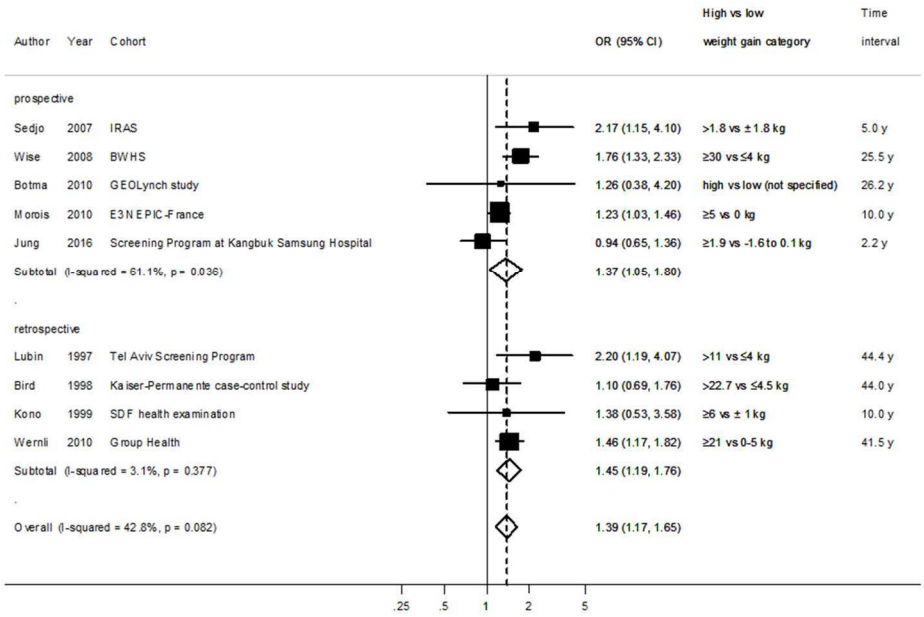
Table 2. Summary odds ratio (OR) and 95% confidence intervals (95% CI) of high versus low meta-analyses of weight gain and occurrence of colorectal adenomas by subgroups

	Summary RR (95% CI)	*N*	I^2 (%)	P_{within} [a]	$P_{between}$ [b]
All studies	1.39 (1.17-1.65)	9	43	0.08	
Study design					
Prospective	1.37 (1.05-1.80)	5	61	0.04	0.78
Retrospective	1.45 (1.19-1.76)	4	3	0.38	
Sex					
Men	1.05 (0.71-1.55)	3	0	0.43	0.51
Women	1.36 (1.01-1.83)	4	49	0.12	
Site of adenoma					
Colon	1.27 (1.07-1.51)	3	0	0.80	0.73
Rectum	1.20 (0.93-1.55)	2	0	0.49	
Time of weight assessment					
Early adulthood	1.40 (1.10-1.77)	6	51	0.07	0.93
Mid-life adulthood	1.40 (1.00-1.95)	3	30	0.24	
Definition of high weight gain category					
<10 kg	1.24 (0.95-1.63)	4	42	0.16	0.21
≥ 10 kg	1.55 (1.26-1.90)	4	31	0.05	
Geographic area					
Asia	1.36 (0.76-2.45)	3	64	0.06	0.61
Europe	1.23 (1.04-1.46)	2	0	0.97	
USA	1.54 (1.26-1.89)	4	28	0.25	
Reference category					
Weight loss included	1.59 (1.19-2.12)	4	26	0.26	0.32
Stable weight	1.30 (1.07-1.58)	5	42	0.14	
Outcome assessment					
Colonoscopy	1.36 (1.12-1.65)	7	38	0.14	0.47
Sigmoidoscopy	1.10 (0.69-1.76)	1	-	-	
Self-reported	1.76 (1.33-2.33)	1	-	-	
Indication					
Without indication	1.40 (1.11-1.76)	7	56	0.04	0.92
With indication	1.45 (1.17-1.81)	2	0	0.81	
Adjustment for weight, BMI, waist circumference					
Yes	1.33 (1.06-1.67)	6	54	0.06	0.59
No	1.47 (1.23-1.76)	3	0	0.96	
Adjustment for physical activity					
Yes	1.51 (1.20-1.90)	4	55	0.08	0.25
No	1.25 (1.02-1.52)	5	10	0.35	
Adjustment for smoking status					
Yes	1.38 (1.15-1.66)	7	45	0.09	0.85
No	1.35 (1.01-1.80)	2	11	0.29	

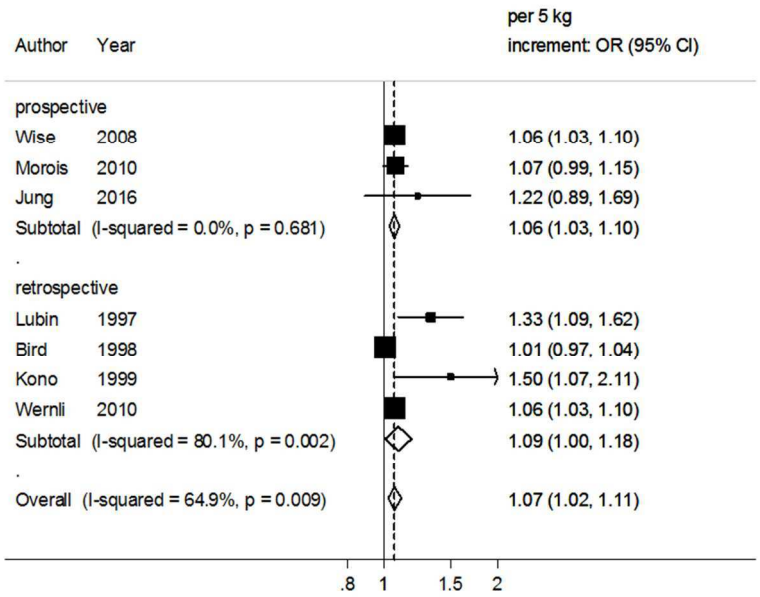
Adjustment for alcohol intake					
Yes	1.31 (1.15-1.50)	4	0	0.70	0.78
No	1.40 (1.06-1.85)	5	60	0.04	
Adjustment for family history colorectal cancer					
Yes	1.34 (1.08-1.65)	4	65	0.03	0.68
No	1.44 (1.14-1.82)	5	0	0.57	

[a] P_{within}, *P* for heterogeneity within each subgroup

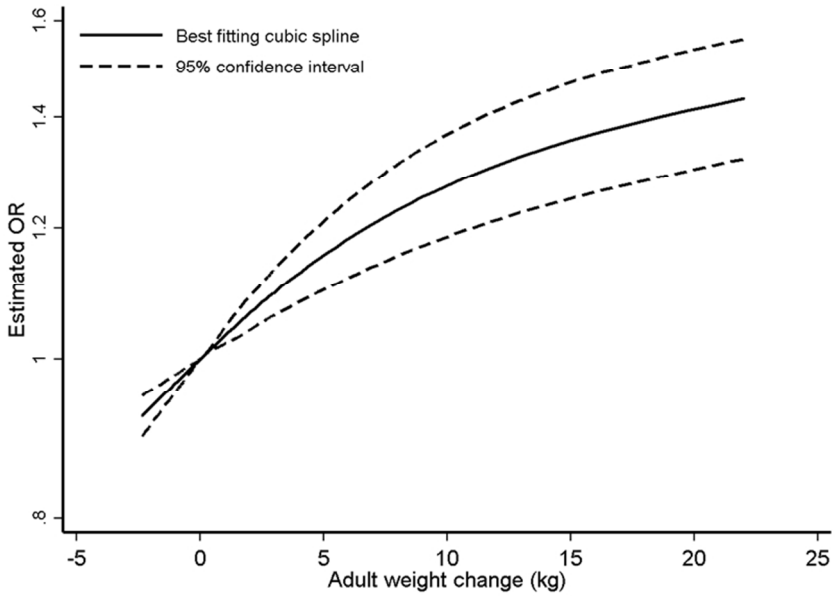
[b] $P_{between,}$ *P* for heterogeneity between subgroups with meta-regression



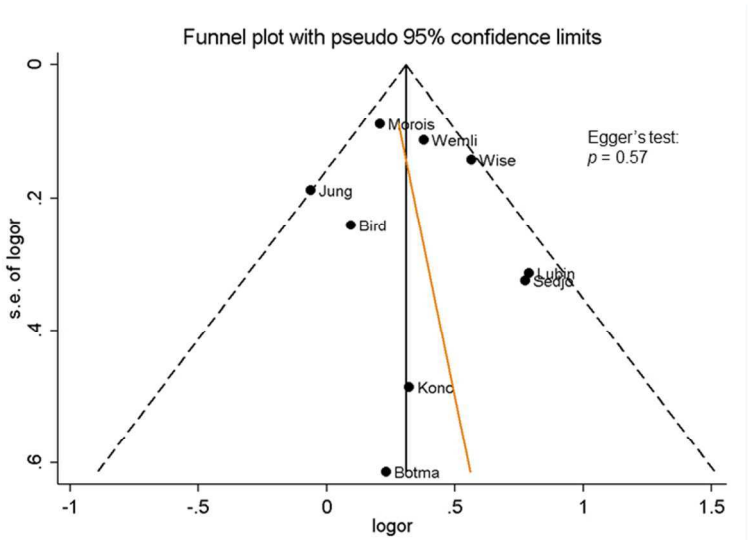
Supplementary figure S1: High vs low meta-analysis for weight gain and adenoma occurrence stratified by study design (*p* for heterogeneity by study design=0.78)



Supplementary figure S2: Dose-response meta-analysis for weight gain per 5 kg and adenoma occurrence stratified by study design (*p* for heterogeneity by study design=0.78)



Supplementary figure S3: Non-linear dose-response meta-analysis for weight gain and adenoma occurrence, only including prospective studies (n =3 studies; $p_{\text{non-linearity}}$ <0.001)



Supplementary figure S4: Funnel plot of studies included in the high vs low meta-analyses of weight gain and adenoma occurrence