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Article:

Schlesinger, S, Aleksandrova, K, Abar, L et al. (8 more authors) (2017) Adult weight gain and colorectal adenomas – a systematic review and meta-analysis. *Annals of Oncology*, 28 (6). pp. 1217-1229. ISSN 0923-7534

<https://doi.org/10.1093/annonc/mdx080>

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<https://doi.org/10.1093/annonc/mdx080>

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4 1 **Article type:** Review
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8 2 **Title:** Adult weight gain and colorectal adenomas – a systematic review and meta-analysis
9

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3 **Abstract.**
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1 **Key words:** Body weight gain, body weight change, colorectal adenomas, polyps, meta-analysis,
2 observational studies

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

1 Introduction.

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

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

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

11 12 **Materials and Methods.**

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

15 *Literature Search*

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

1 identified using PubMed, a change in the protocol was made and only PubMed was used for the
2 updated searches. The literature search included two outcomes, colorectal cancer and colorectal
3 adenomas. As this systematic review and meta-analysis focus on colorectal adenomas only, we
4 excluded studies on colorectal cancer. We conducted an update of the literature search in
5 Medline (PubMed) for articles on adult weight change and colorectal adenomas until September
6 2016.

8 *Study selection*

9 Studies were selected if they 1) reported on the association between adult weight change
10 and adenoma occurrence or recurrence, 2) used a cohort, nested case-control, case-cohort, case-
11 control, cross-sectional design, or follow-up studies of randomized clinical trials, and 3)
12 provided effect estimates for this association (including hazard ratio or odds ratio (OR)) with the
13 95% confidence interval (95% CIs). For simplicity, we use the term OR for all these estimates in
14 the present manuscript. In addition, we defined studies as prospective if a follow-up period
15 between second weight assessment and diagnosis of colorectal adenomas was available and as
16 retrospective if the second weight measure was taken at time of colorectal adenoma assessment
17 or recalled 1 year before. We focused on two different outcomes: adenoma occurrence (no
18 previous adenoma was known) and adenoma recurrence (prior adenoma was diagnosed). Studies
19 not published as original articles were excluded. Furthermore, we excluded one study reporting
20 on changes of BMI instead of weight change because a conversion into weight change was not
21 possible.[31]

23 *Data extraction*

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

9 10 *Statistical analysis*

11 The associations between weight gain during adulthood and colorectal adenoma
12 occurrence or recurrence were analyzed by comparing extreme categories of weight gain during
13 adulthood (high weight gain vs. low weight gain), and summary ORs (95% CI) were calculated
14 by applying random effects models. Two studies reported on adult weight gain in pounds,[24,
15 26] and quantifications were converted in kg (1 kg \cong 2.2 lbs). For one study, we converted adult
16 weight change in kg/year into weight change per kg by multiplying the quantification with the
17 time interval between both weight assessments.[28] If stable weight was not used as reference
18 category in single studies,[21, 23] we used the method of Hamling *et al.* to convert risk estimates
19 to being relative to this reference category.[32] For studies that reported estimates stratified by
20 sex,[22] or adenoma site (colon, rectal and both),[29] a fixed effect model was used to combine
21 the estimates for the main analysis.

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

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

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

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

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

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

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

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16 **Results.**

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

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22 *Adenoma Occurrence*

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

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

8 Subgroup analyses are shown in **Table 2**. The findings stratified by sex suggested that the
9 association was stronger in women [summary OR (95% CI) 1.36 (1.01-1.83); $N=4$ studies]
10 compared to men [summary OR (95% CI) 1.05 (0.71-1.55); $N=3$ studies], but differences were
11 not statistically significant (P for heterogeneity by sex=0.51). When we restricted the stratified
12 analysis by sex to studies providing both information (for men and women separately, $N=2$
13 studies), the summary OR for women was 0.78 (95% CI: 0.31-1.95) and for men 1.15 (95% CI:
14 0.46-2.86), with no indication for interaction (P for heterogeneity by sex=0.68). Stronger
15 associations were observed for studies which defined high adult weight gain as greater or equal
16 than 10 kg [summary OR (95% CI) 1.55 (1.26-1.90)] compared to studies investigating less than
17 10 kg [summary OR (95% CI) 1.24 (0.95-1.63)]; but differences were not statically significant
18 (P for heterogeneity by weight gain category=0.21). We did not observe a difference of the
19 association after stratification by study design (prospective vs. retrospective studies) (**Table 2**
20 and **Supplementary figure S1**) and adjustment for excess body weight (**Table 2**).

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

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

3 For the dose-response meta-analysis we included 7 studies.[20, 21, 23, 25, 27-29] Per
4 each 5 kg weight gain during adulthood the odds of colorectal adenoma was increased by 7%
5 (95% CI: 2%-11%) (**Figure 3**). There was moderate to high heterogeneity (I^2 : 65%,
6 $P_{heterogeneity}=0.009$), In a sensitivity analysis, excluding studies using a combination of adult
7 weight gain and weight loss in the reference category,[23, 28, 29, 38] the odds of colorectal
8 adenoma was slightly higher [summary OR (95% CI) per 5 kg weight gain during adulthood:
9 1.08 (1.03-1.12), $N=4$ studies)] and there was no indication for heterogeneity between the
10 studies (I^2 : 0%, $P_{heterogeneity}=0.87$). No differences by study design (prospective vs retrospective)
11 was observed (**Supplementary figure S2**). The non-linear dose-response curve indicated
12 evidence of non-linearity ($P_{non-linearity}<0.001$), but no threshold of adult weight gain in relation to
13 risk increase was observed. The curve shows an increase odds of colorectal adenoma throughout
14 all the range of adult weight gain investigated, although the curve was steeper at lower levels of
15 weight gain than at higher levels (**Figure 4**). After restricting our non-linear dose-response meta-
16 analysis to prospective studies only, findings did not change substantially (**Supplementary**
17 **figure S3**). When we considered the time interval of weight gain during adulthood, the odds of
18 colorectal adenoma was 30 % increased by each kg adult weight gain per year [summary OR
19 (95% CI) for 1 kg/y: 1.30 (1.10-1.55); I^2 : 70%, $P_{heterogeneity}=0.003$].

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

22
23 *Adenoma Recurrence*

1 For the analysis on weight gain during adulthood and adenoma recurrence we included 3
2 studies (2 retrospective and 1 prospective studies),[22-24] including 1,350 cases among 5,559
3 participants. One study reported on weight gain during early adulthood and 2 on weight gain
4 during mid-life. The summary OR (95% CI) in high versus low meta-analysis was 1.14 (0.88-
5 1.49), without statistically significant indication of heterogeneity between studies ($I^2=48\%$,
6 $P_{heterogeneity}=0.15$) (**Figure 2**). We did not conduct subgroup analyses, linear and non-linear dose-
7 response meta-analysis of weight gain and adenoma recurrence because of the limited number of
8 studies.

10 **Discussion.**

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

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

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

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

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

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

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3 1 the null. Fourth, the analysis on adenoma recurrence and subgroup analyses by sex and adenoma
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5 2 site were restricted by the small number of studies providing the information separately. These
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8 3 findings should be interpreted with caution and more studies investigating sex- and site-specific
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10 4 associations between adult weight gain and colorectal adenoma occurrence and recurrence are
11
12 5 warranted.

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15 6 In conclusion, this meta-analysis indicated evidence that weight change during adulthood
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17 7 is associated with colorectal adenoma occurrence independently of excess body weight. In the
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19 8 non-linear dose-response meta-analysis, colorectal adenomas were less common in individuals
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21 9 reporting weight loss and more common in individuals with weight gain. Even a small amount of
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23 10 adult weight gain was related to higher odds of colorectal adenoma. Our findings show the
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25 11 benefits of weight control from early adulthood regarding the occurrence of colorectal adenomas
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28 12 – a known precursor of colorectal cancer – which might be relevant for early prevention.
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1 **Funding:** The work of DSMC, LA, ARV, SV, EP, CATS and TN was supported by the World
2 Cancer Research Fund International as part of the Continuous Update Project (grant number:
3 2007/SP01). The work of SS and DA was supported by a NHS BRC grant (Interventional Public
4 Health). The views expressed in this review are the opinions of the authors. The views may not
5 represent the views of World Cancer Research Fund International/ American Institute for Cancer
6 Research and may differ from those in future updates of the evidence related to food, nutrition,
7 physical activity, and cancer risk. The sponsor of this study had no role in the decisions about the
8 analysis or interpretation of the data; or preparation, review, or approval of the manuscript.

9
10 **Disclosures:** The authors have declared no conflicts of interest.

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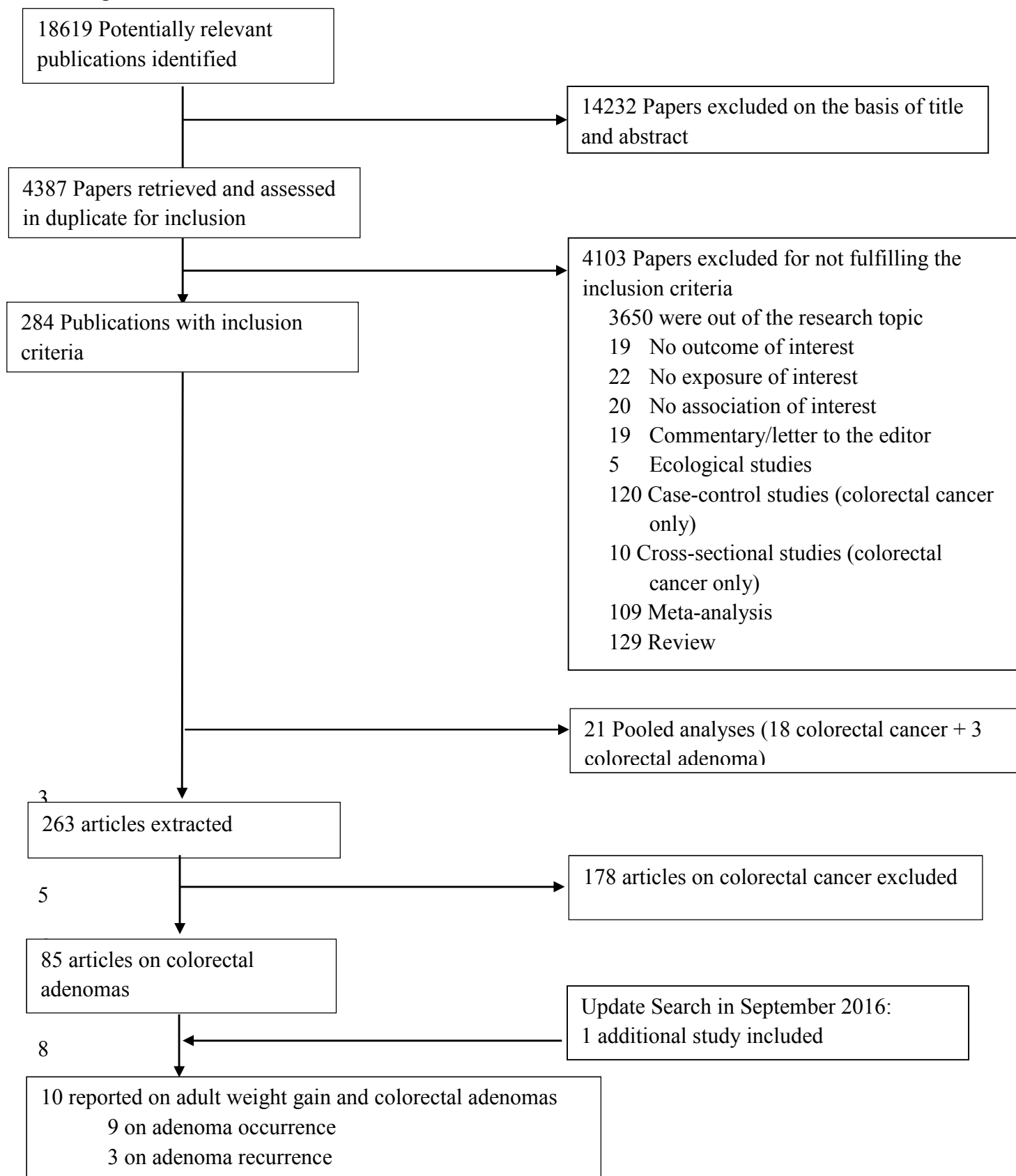
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6 2 Figure 1: Flow chart of study selection
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8 3 Figure 2: High vs low meta-analysis for weight gain and colorectal adenoma occurrence and
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12 5 Figure 3: Dose-response meta-analysis for weight gain per 5 kg and colorectal adenoma
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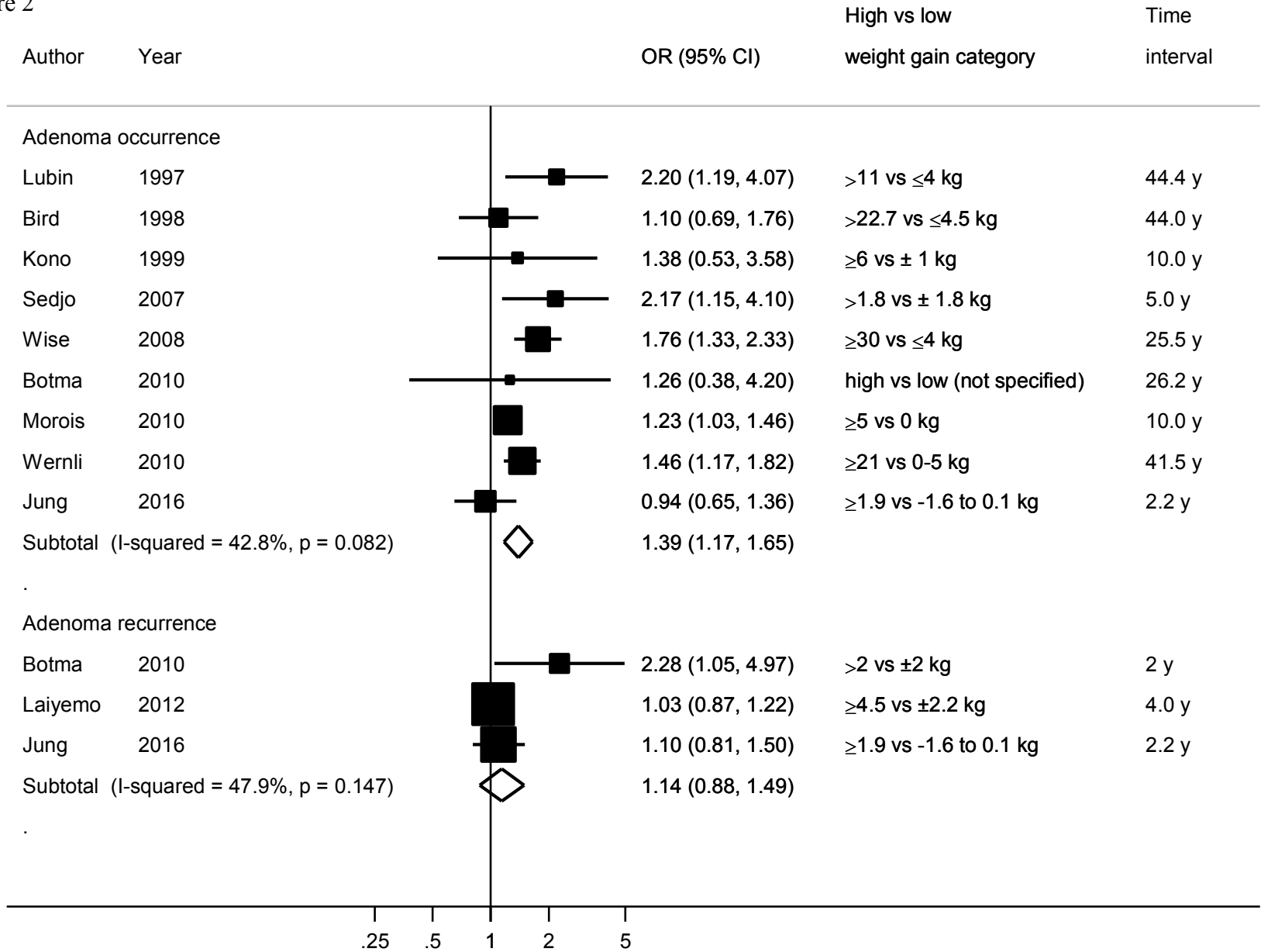
17 7 Figure 4: Non-linear dose-response meta-analysis for weight gain and colorectal adenoma
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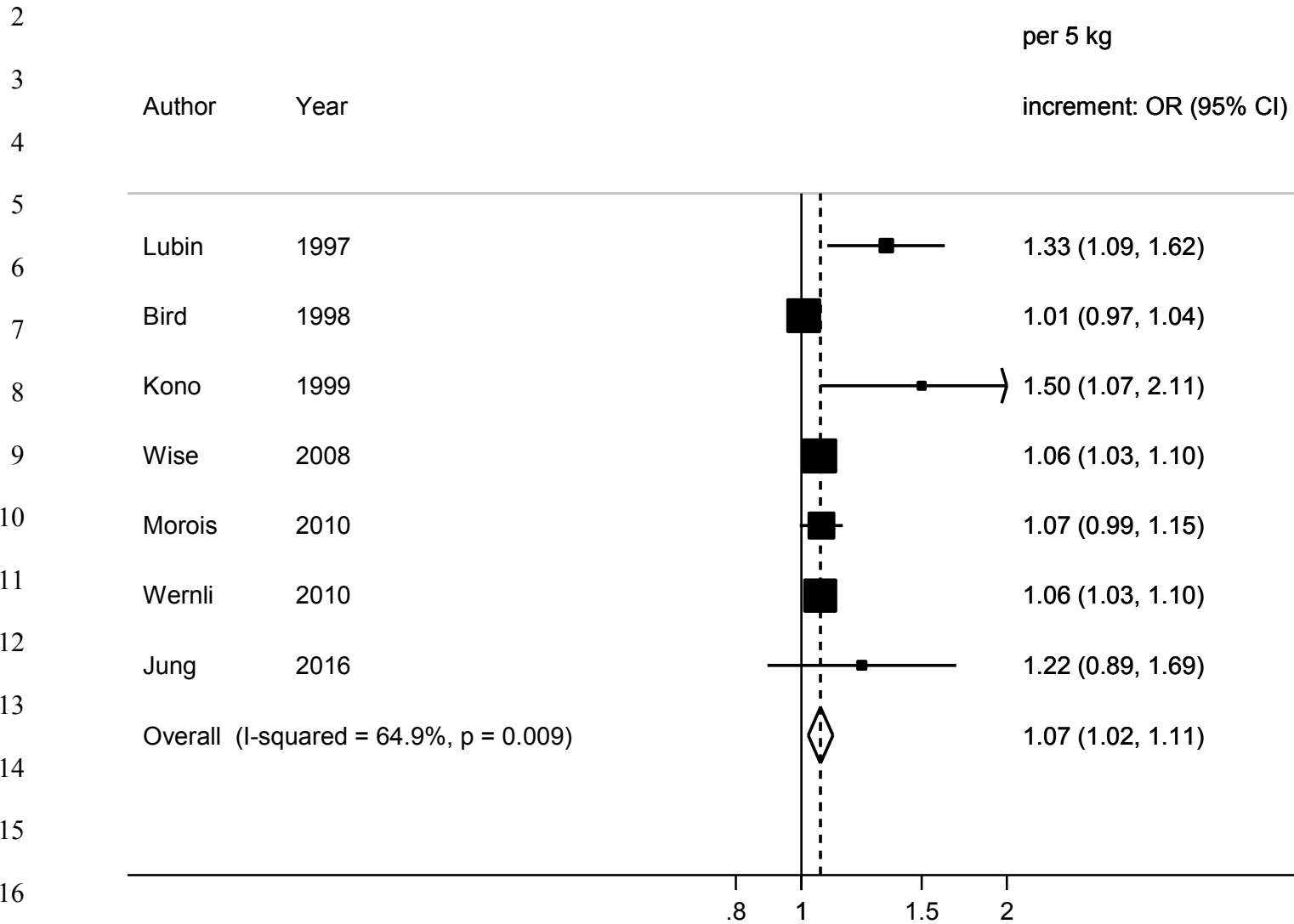
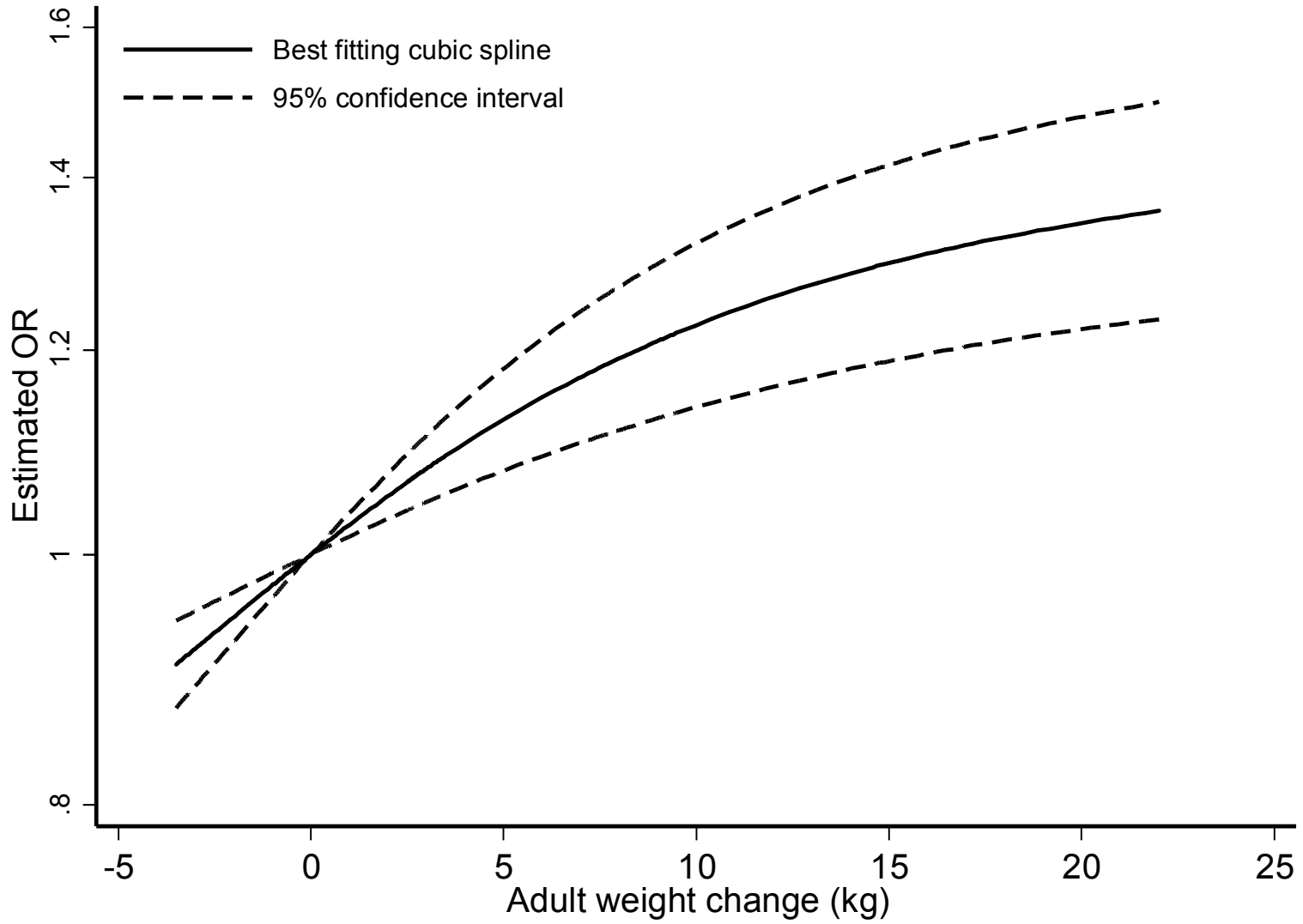
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Figure 4.



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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 lbs loss (5-9 lbs) no change (ref) 5-9 lbs ≥10 lbs	≤-10 lbs: 0.91 (0.77-1.07) -5- -9 lbs) 0.90 (0.76-1.07) no change: 1 (ref) 5-9 lbs: 0.97 (0.82-1.16) ≥10 lbs: 1.03 (0.87-1.23)	age, sex, NSAID use, smoking status, baseline weight, dietary randomized assignment, family history of CRC
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Adenomas:**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)**Recurrence:****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)Jung, 2016
(Korea)[23]Health screening
program at Kangbuk
Samsung Hospital,
Retrospective study,
2.2 yM & F,
41.2 ycolorectal
adenomas and
recurrence,
colonoscopyN: 3,121
without and
2,176 with
adenoma
Cases: 447
Recurrence:
591measured 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 kgAge, 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)[2 2]	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

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

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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

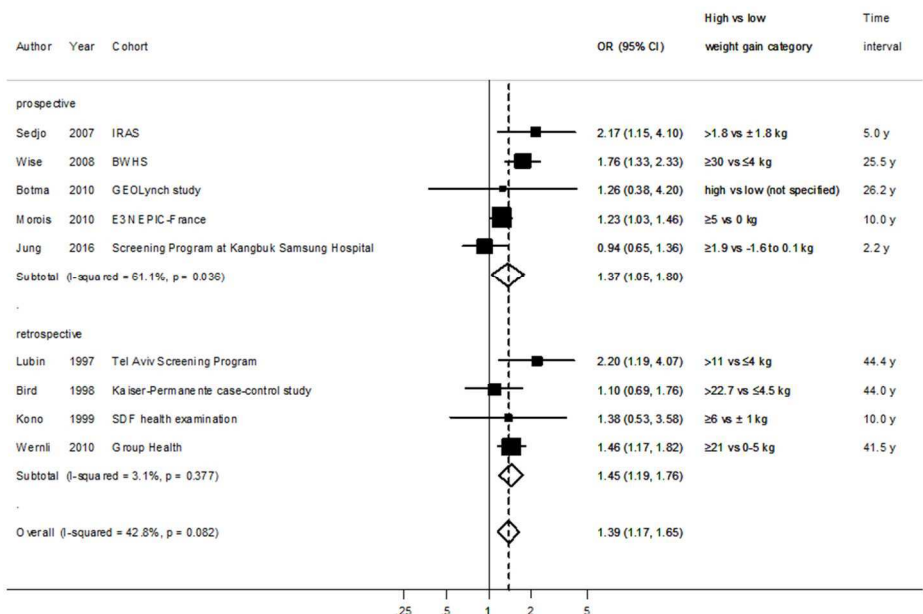
^b $P_{between}$, P for heterogeneity between subgroups with meta-regression

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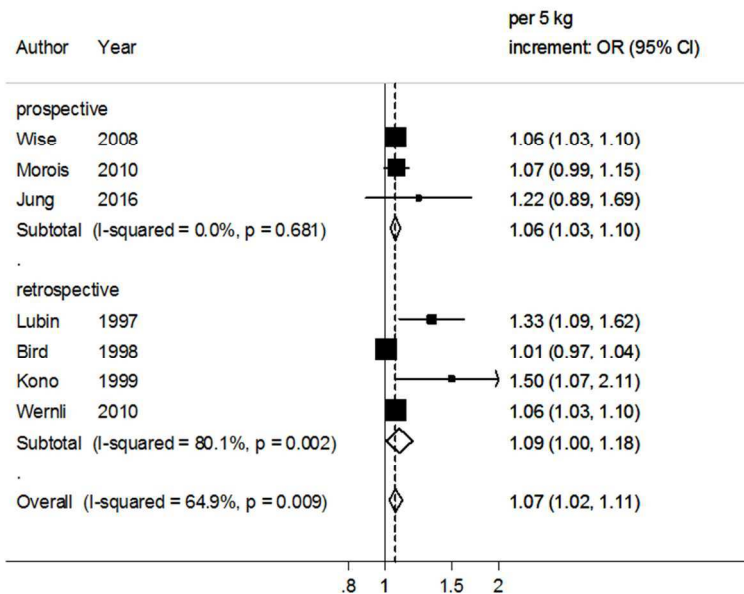
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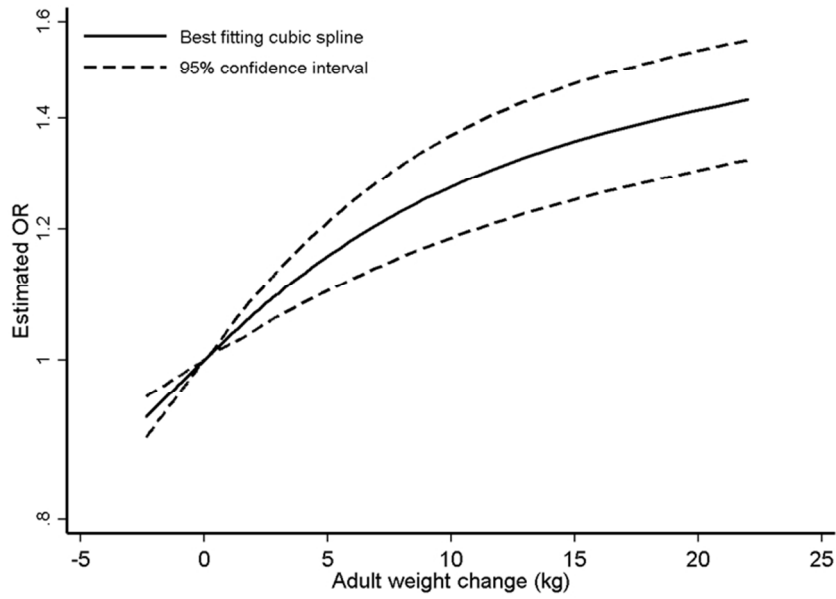


Supplementary figure S1: High vs low meta-analysis for weight gain and adenoma occurrence stratified by study design (p for heterogeneity by study design=0.78)



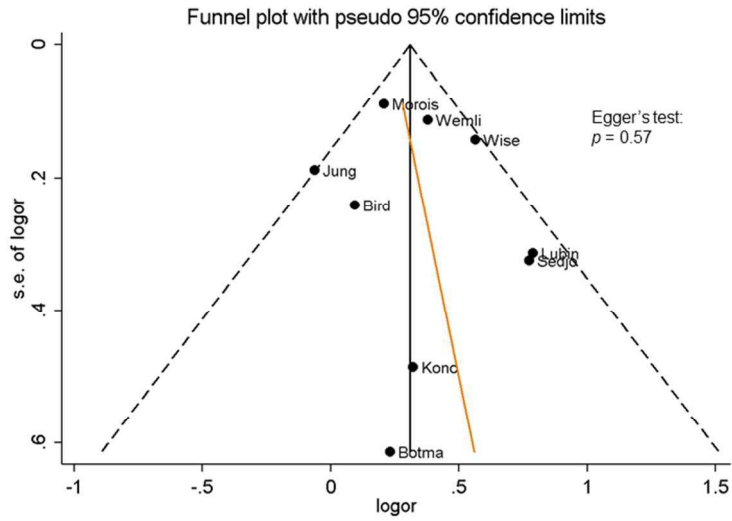
Supplementary figure S2: Dose-response meta-analysis for weight gain per 5 kg and adenoma occurrence stratified by study design (p for heterogeneity by study design=0.78)

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

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

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