see related editorial on page 1187

CME

REVIEW

Body Mass Index Category as a Risk Factor for Colorectal Adenomas: A Systematic Review and Meta-Analysis

Koji Okabayashi, MD[1,2], Hutan Ashrafian, MBBS, MRCS[1], Hirotoshi Hasegawa, MD, FRCS[2], Jae-Hoon Yoo, MD[3], Vanash M. Patel, MBBS, MRCS[1], Leanne Harling, MBBS, MRCS[1], Simon P. Rowland, BSc (Hons), MBBS[1], Mariam Ali, BSc (Hons)[1], Yuko Kitagawa, MD, PhD[2], Ara Darzi, PC, KBE, MD, FRCSI, FRCS, FMedSci[1] and Thanos Athanasiou, MD, PhD, FRCS, FETCS[1]

OBJECTIVES: **The association between increasing body weight and colorectal adenoma prevalence has been suggested to follow a similar pattern to excess weight and colorectal cancer, although the magnitude of this relationship has not been validated. The objective of this study was to quantify the association and dose–response relationship between body mass index (BMI) and colorectal adenoma prevalence in clinical trials.**

METHODS: **We systematically reviewed 23 studies (168,201 participants), which compared the prevalence of colorectal adenomas according to World Health Organization BMI categories. We assessed the effects of each BMI category on colorectal adenomas where odds ratio (OR) was used as a surrogate for effect size, and applied multivariate meta-analysis as a method of sensitivity analysis to evaluate the robustness of our findings and to analyze adenoma prevalence by multiple BMI categories simultaneously to assess for a dose–response relationship. Heterogeneity and publication bias were assessed.**

RESULTS: **Subjects with a BMI of ≥25 had a significantly higher prevalence of colorectal adenomas (OR = 1.24 (95% confidence interval (CI): 1.16–1.33), $P<0.01$) when compared with those with BMI < 25. Multivariate meta-analysis also confirmed a positive association between higher BMI categories and the prevalence of colorectal adenoma (BMI: 25–30 vs. BMI < 25; OR = 1.21 (95% CI: 1.07–1.38), $P<0.01$; BMI≥30 vs. BMI < 25; OR = 1.32 (95% CI: 1.18–1.48), $P<0.01$) and revealed a dose–response relationship.**

CONCLUSIONS: **The positive association between obesity and colorectal adenoma prevalence demonstrates an underlying dose–response relationship according to BMI. Colorectal centers may benefit from the timely screening of obese patients for colorectal adenomas in addition to clarifying the biological role of adiposity on colorectal tumor initiation and progression.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

The global epidemic of patients with excess weight and obesity continues to escalate and impose a huge burden on global health-care systems through chronic disease and disability. According to the World Health Organization (WHO), obesity rates are increasing by 30 million cases per year with at least 300 million people who are clinically obese and 1.4 billion adults who are overweight (1,2). Colorectal cancer (CRC) is also a global concern as it is the third most common cancer worldwide, accounting for ~1 million new cases in 2002 (9.4% of the world total) (3). The etiology of CRC includes both genetic and environmental factors although most cases are sporadic (4). The mechanistic steps of CRC development correspond to an adenoma-carcinoma sequence resulting from the accumulation of cancerous genetic changes (5,6).

Increased body weight and obesity are now recognized as environmental factors, which can contribute to the development of CRC. The mechanisms associating obesity with CRC include

[1]Department of Surgery and Cancer, Imperial College London, London, UK; [2]Department of Surgery, Keio University, School of Medicine, Tokyo, Japan; [3]Department of Surgery, National Hospital Organization Saitama National Hospital, Saitama, Japan. **Correspondence:** Thanos Athanasiou, MD, PhD, FRCS, FETCS, Department of Surgery and Cancer, Imperial College London, 10th Floor QEQM-Building, Praed Street, London W2 1NY, UK. E-mail: t.athanasiou@imperial.ac.uk
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the release of growth factors and steroids within an environment of chronic inflammation and insulin resistance (7). The WHO defines overweight and obesity ranges according to the body mass index (BMI≥25 kg/m^2 is classed as overweight and BMI≥30 kg/m^2 is classed as obese, whereas patients with a BMI ranging between 18.5 and 24.99 kg/m^2 are considered to be in the normal range of body weight) (2). A recent meta-analysis has demonstrated a significant association between raised BMI and CRC (8), and has highlighted the increased risk of CRC with obesity. Consequently, national health-care authorities including the American College of Gastroenterology have highlighted that obese patients may benefit from early CRC screening (perhaps as early as 45 years old) (9).

The development of colorectal adenomas is an important precursor to the subsequent development of CRC; however, the relationship between excess weight and colorectal adenoma formation has not yet been systematically assessed. An increased understanding between the development of colorectal adenomas and BMI categories can clarify the mechanistic steps linking adiposity and CRC and may be useful in determining the benefits of early CRC screening. The aim of this systematic review is to quantify the association between BMI categories and colorectal adenoma prevalence in clinical trials.

METHODS

This review was written based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (10).

Literature searching strategy

We systematically searched EMBASE (from 1980 to August 2011), MEDLINE (from 1950 to August 2011), and PsycINFO (from 1967 to August 2011) for manuscripts that mentioned the relationship between obesity and the prevalence of colorectal adenoma without language restriction. Our search terms consisted of three main components, colorectal (*colorectal* OR *colon* OR *colonic* OR *rectum* OR *rectal*) AND disease (*neoplasm* OR *polyp* OR *adenoma*) AND obesity or overweight (*body mass index* OR *BMI* OR *body size* OR *body weight* OR *intraabdominal* OR *overweight* OR *fat* OR *obesity* OR *obese* OR *waist*).

Inclusion and exclusion criteria

We defined the prevalence of colorectal adenoma as a primary end point of this study. As several studies have reported on the combined outcomes of adenomas, cancer, and hyperplastic polyps, we selected studies including >90% of colorectal adenoma patients among all colorectal polyp patients to reduce the risk of bias. We included cohort studies that determined overweight or obesity through BMI according to the WHO classification (2). We recorded the prevalence of colorectal adenoma cases during follow-up, reported risk estimates (relative risks, odds ratios (ORs), or hazard ratios) and 95% confidence intervals (CIs) or sufficient data to estimate these. We also included case–control studies nested in cohort studies and control arms of clinical trials, which included consecutive cases. On the other hand, case-matched control studies and those, in which no inclusion and/or exclusion criteria were presented, were excluded because they could not provide information for estimation of adenoma prevalence. We excluded experimental studies, unpublished studies, and those including patients with hyperplastic polyps and serrated adenomas. The eligibility of studies was assessed independently by two investigators (K.O. and H.A.). We attempted to contact authors of studies with some missing data to obtain additional information or to confirm our final results.

Assessment of methodological quality and data extraction

We extracted data based on the characteristics of study design, participants and covariates together with the outcomes of the prevalence of colorectal polyps or adenoma for each category of baseline BMI measurement. The quality of included studies was assessed independently by two assessors (K.O. and H.A.) according to the Newcastle-Ottawa Scale (11,12). The main items for study quality scoring were as follows: (i) representativeness (one point was given if participants were not restricted); (ii) selection of non-exposed cohort (one point was given if they were consecutive or clearly a representative series of cases); (iii) ascertainment (one point was given if their BMI was measured by nurses and other medical staffs); (iv) demonstration of selection (one point was given if they stated no history of colorectal adenoma); (v) comparability on the basis of the design or analysis (two points were given if there was an adjustment for any covariates in the statistical analysis and one point was given if there was unadjustment for any covariates); (vi) assessment (one point was given if they were based on medical records); (vii) duration of follow-up (one point was given to all the study because they were based on cross-sectional study); and (viii) adequacy (one point was given to all the study because they were based on cross-sectional study). Scores ranged from 0 (lowest) to 9 (highest). Studies with scores ≥7 were classified as "higher" quality and those with scores <7 were classified as "lower" quality.

Statistical methods

We performed random effects direct comparison meta-analysis applying OR as a surrogate for effect size. We calculated 95% CIs and quantified between-study heterogeneity with the I^2 index (13). To assess for publication bias, we tested for funnel plot asymmetry using the regression test by Egger (14) and Begg (15) and estimated the number of studies missing from a meta-analysis using the trim and fill method (16). We assessed the influences of several covariates to the generated heterogeneity of ORs using random-effects meta-regression. We also used subgroup analysis for study quality, ethnicity, gender and degree of progression, and meta-regression to assess the effect of adjustment for the key covariates of year of publication, prospective study, Asian ethnicity, sample size, average age, method of confirmation, percentage female, family history, current smoking, current drinking, and obesity.

We also performed multivariate meta-analysis as part of sensitivity analysis to assess the robustness of our findings and to

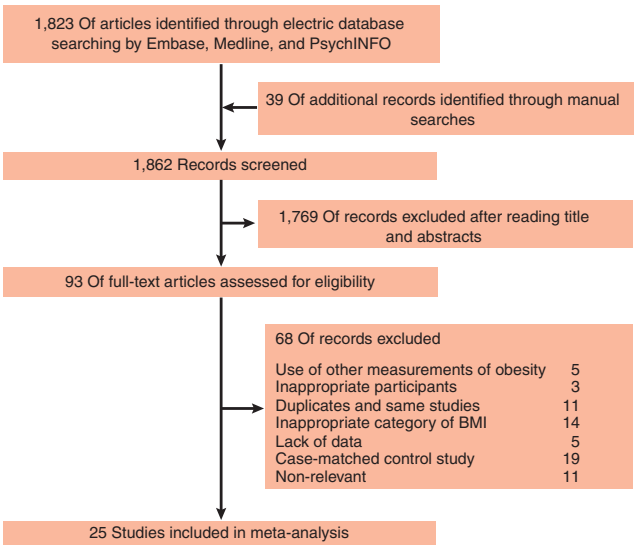

Figure 1. Overview of the selection process. BMI, body mass index.

analyze adenoma prevalence by multiple BMI categories simultaneously. This could clarify the dose–response influence of BMI on the prevalence of colorectal adenomas. We included studies reporting on adenoma prevalence based on more than three BMI categories. The calculated dependent variables were the ORs for BMI 25–30 and BMI≥30, compared with BMI < 25. We defined the within-study correlation adenoma prevalence as zero because of our assumption that similar to diagnostic studies, our outcomes of interest (categorized by BMI category) are independently derived from separate patients (17).

Multivariate meta-analysis was performed by Stata version 10 (StataCorp, College Station, TX), all other statistical analyses were conducted with the statistical package R version 2.12.2 (The R Foundation for Statistical Computing, Vienna, Austria). For all comparisons, except those for heterogeneity, statistical significance was defined as $P < 0.05$, and all tests were two-sided.

RESULTS

Search process

The overview of our search process is demonstrated in **Figure 1**. We found 1,823 articles from electronic searches and 39 from other sources. We excluded 1,769 studies after removing duplicates from the title and abstract search. Ninety-three manuscripts were reviewed in full text and twenty-five manuscripts (18–42) met our search criteria. Details of studies included are listed in **Table 1**, while those of studies excluded are listed in **Supplementary Table 1** online. Included studies consisted of 2 nested cohorts from randomized control studies (28,34), 19 large-scale prospective cohort studies (18–20,22–25,27,29–32,36–42), and four large retrospective studies (21,26,33,35). The quality of all included studies by Newcastle-Ottawa Scale is assigned to 16 (18,20–23,25–28,30,32,36,37,40–42) as higher and 9 (19,24,29,31,33–35,38,39) as lower (**Table 2**). The confirmation of colorectal adenoma was based on pathological findings following endoscopic biopsy and excision in 23 studies (18,20–29,31–42) and periodic self-reported questionnaires in 2 studies (19,30).

Prevalence of colorectal adenomas

Twenty-three studies reported on the prevalence of colorectal adenomas (18–40). These studies included a total of 105,190 participants, 63,011 who were defined as BMI < 25 and 42,179 who were defined as BMI≥25. Pooled weighted prevalence of colorectal polyps were 19% (95% CI: 16–22) in BMI < 25 and 22% (95% CI: 18–26) in BMI≥25. The comparison between BMI < 25 and BMI≥25 demonstrated that subjects with a BMI of ≥25 had a significantly higher OR of colorectal adenomas (OR = 1.24 (95% CI: 1.16–1.33), $P < 0.01$) with moderate heterogeneity ($I^2 = 58.9\%$; **Figure 2**). The tests for funnel plot asymmetry by Egger's test and Begg's test identified no publication bias (Egger's test; bias = −1.15, $P = 0.25$, Begg's test; Kendall's tau = −0.15, $P = 0.32$). Although funnel plot assessment identified one extreme outlier, the trim and fill analysis demonstrated no missing study in the funnel plot (**Figure 3**). Furthermore, we excluded the effect of one extreme outlier (the oldest manuscript studied (29)) and performed an analysis of the remaining 24 studies which resulted in a change of OR of colorectal adenomas to OR = 1.27 (95% CI: 1.21–1.34, $P < 0.01$). Subsequent analysis by univariate meta-regression revealed that including this outlier study identified publication year as a significant contributor to the association between raised BMI and adenoma prevalence. Conversely, the exclusion of this one study resulted in a non-significant effect of publication year on the association between BMI and adenoma prevalence. With regards to study design, cross-sectional asymptomatic screening populations are better to examine certain issues such as prevalence. We therefore performed further analysis using 21 studies that only included asymptomatic screening cohorts. This analysis demonstrated that overweight was still a significant risk factor of colorectal adenoma formation (OR = 1.24 (95% CI: 1.14–1.35), $P<0.01$).

Subgroup analysis

Study quality. The impact of study quality on OR was assessed. ORs were 1.23 (95% CI: 1.14–1.31, $P < 0.01$) in higher quality studies and 1.20 (95% CI: 1.00–1.44, $P = 0.05$) in lower quality studies. A positive correlation between overweight and the prevalence of colorectal adenoma was consistent regardless of study quality, and furthermore there was no significant difference between study quality ($P = 0.98$) (**Figure 4**).

Ethnicity. To explore differences of ORs in adenoma prevalence between Asian and Western ethnicities, we categorized all studies into two groups, those published in Western countries and those published in Asian countries. ORs were 1.18 (95% CI: 1.04–1.34, $P = 0.01$) in Western countries and 1.35 (95% CI: 1.27–1.44, $P < 0.01$) in Asian countries, respectively. A positive correlation between overweight and the prevalence of colorectal adenoma was consistent regardless of ethnicity, and furthermore there was no significant difference between study quality ($P = 0.11$) (**Figure 4**).

Table 1. Overview of included studies

Author	Year	Design	Country	Enrolment	No. of patients	BMI category	BMI determinant	Percentage of adenoma	Percentage of cancer	Definition of advanced adenomaa	Procedure of ascertainment of adenoma	Total colono-scopy	Asymptomatic cohort
Mannes	1986	Pros	Germany	1982–1983	842	<25, ≥25	NS	100	0		Scope	Yes	Yes
Giovan-nucci	1996	Pros	USA	1976	13,057	<21, 21–22, 23–24, 25–28, >29	Questionnaire	100	0		Questionnaire	No	No
Lieberman	2003	Pros	USA	1994–1997	1,770	<25, 25–27, 28–29, 30–33, ≥33	NS	100	0	A	Scope	Yes	Yes
Guilera	2005	Pros	USA	1998–2003	720	<25, 25–30, ≥30	Measurement	100	0		Scope	Yes	Yes
Kim CS	2005	Pros	South Korea	2002	575	<23, 23–25, ≥25	Measurement	100	0		Scope	No	Yes
Purdue	2005	RCT	USA	1993–2001	20,671	<25, 25–30, ≥30	Questionnaire	100	0		Scope	No	Yes
Larsen	2006	RCT	Norway	2001–2001	3,972	<25, 25–30, ≥30	Questionnaire	98.5	1.5	A	Scope	Yes	Yes
Teetzmann	2006	Pros	Germany	1998–2004	295	18.5–25, 25–30, ≥30	NS	100	0		Scope	Yes	Yes
Anderson	2007	Pros	USA	1999–2005	2,493	<25, 25–30, 30–40,≥40	NS	100	0		Scope	Yes	Yes
Ji	2007	Pros	South Korea	2002–2005	5,848	<25, ≥25	NS	100	0		Scope	No	Yes
Kim SE	2007	Pros	South Korea	2005–2005	1,697	<25, ≥25	Measurement	100	0	A	Scope	Yes	Yes
Sedjo	2007	Pros	USA	2002–2004	600	<25, 25–30, ≥30	Measurement	100	0	A	Scope	Yes	Yes
Steinmetz	2007	Pros	France	1998–2003	5,452	<25, 25–30, ≥30	Measurement	100	0	B	Scope	Yes	No
Wolf	2007	Pros	USA	1991–1994	593	<25, 25–30, ≥30	Measurement/ questionnaire	100	0	B	Scope	No	No
Nam JH	2008	Pros	South Korea	2005–2006	253	<23, 23–25, ≥25	NS	100	0		Scope	Yes	Yes
Leitzmann	2009	Pros	USA	1999–2002	1,420	<25, 25–30, ≥30	NS	94.7	5.3	A	Scope	Yes	Yes
Omata	2009	Retro	Japan	N.S	870	<22, 22–25, ≥25	Questionnaire	92.8	2.6		Scope	Yes	No
Sato	2009	Retro	Japan	1992–2006	15,380	<25, ≥25	NS	100	0		Scope	Yes	Yes
Hassan	2010	Retro	Italy	2002–2003	1,321	<25, ≥25	Questionnaire	99.5	0.5		Scope	Yes	Yes
Hong	2010	Pros	South Korea	2005–2009	1,761	<23, 23–25, ≥25	Questionnaire	100	0	A	Scope	Yes	Yes
Huang	2010	Pros	China	2008–2009	2,690	<18.5, 18.5–25, ≥25	Questionnaire	100	0	A	Scope	Yes	Yes
Kim KS	2010	Retro	South Korea	2006–2007	1,316	<25, ≥25	Measurement	100	0	A	Scope	Yes	Yes
Morois	2010	Pros	France	1993	17,391	<18.5,18.5–25, 25–30, 30–35,≥35	Questionnaire	100	0		Questionnaire	No	Yes
Nam SY	2010	Pros	South Korea	2008–2008	3,922	<20, 20–25, 25–30, ≥30	Measurement	100	0		Scope	Yes	Yes
Stein	2010	Pros	USA	2006–2007	600	18–25, 25–30, 30–35, ≥35	Measurement	100	0	A	Scope	Yes	Yes

BMI, body mass index; NS, not stated.

[a]A: Advanced adenoma means an adenoma measuring >10 mm in diameter and/or with villous components and/or showing severe dysplasia, B: Advanced adenoma means >10 mm in diameter.

Table 2. Quality assessment according to the Newcastle-Ottawa scale

Author	Year	Selection				Compara-bility	Outcome			Total score	
		Represent-ativeness	Selection of non-exposed cohort	Ascertain-ment	Demon-stration of selection		Assess-ment	Duration of follow-up	Adequacy		
Mannes	1986	1	1	0	0	0	1	1	1	5	Lower
Giovannucci	1996	0	1	0	0	2	0	1	1	5	Lower
Lieberman	2003	1	1	0	1	2	1	1	1	8	Higher
Guilera	2005	1	1	1	1	2	1	1	1	9	Higher
Kim CS	2005	0	1	1	0	2	1	1	1	7	Higher
Purdue	2005	0	1	0	0	2	1	1	1	6	Lower
Larsen	2006	1	1	0	0	2	1	1	1	7	Higher
Teetzmann	2006	1	1	0	1	0	1	1	1	6	Lower
Anderson	2007	1	1	0	1	2	1	1	1	8	Higher
Ji	2007	0	1	1	0	0	1	1	1	5	Lower
Kim SE	2007	1	1	1	1	0	1	1	1	7	Higher
Sedjo	2007	1	1	1	0	2	1	1	1	8	Higher
Steinmetz	2007	1	1	1	0	0	1	1	1	6	Lower
Wolf	2007	0	1	0	1	2	1	1	1	7	Higher
Nam JH	2008	1	1	0	1	0	1	1	1	6	Lower
Leitzmann	2009	1	1	0	1	2	1	1	1	8	Higher
Omata	2009	1	1	0	1	0	1	1	1	6	Lower
Sato	2009	1	1	0	1	0	1	1	1	6	Lower
Hassan	2010	1	1	0	1	2	1	1	1	8	High
Hong	2010	0	1	0	1	2	1	1	1	7	High
Huang	2010	1	1	0	1	2	1	1	1	8	High
Kim KS	2010	1	1	1	1	0	1	1	1	7	High
Morois	2010	1	1	0	1	2	0	1	1	7	High
Nam SY	2010	1	1	1	1	2	1	1	1	9	High
Stein	2010	1	1	1	1	2	1	1	1	9	High

Gender. Eleven (18,19,27,32,34–38,40,41) studies reporting on the prevalence of colorectal adenoma by gender were identified. ORs were 1.16 (95% CI: 0.94–1.45, $P=0.16$) in men and 1.19 (95% CI: 1.01–1.33, $P=0.03$) in females (**Figure 4**). These results suggested overweight and obesity were significant risk factors of colorectal adenoma in females, but based on subgroup analysis there was no significant difference in adenoma prevalence between sexes ($P=0.90$). Three studies reported the prevalence by menopausal status (27,34,40). Pre-menopausal female status had a higher risk of adenomas (OR = 2.48 (95% CI: 0.56–11.05), $P=0.23$) when compared with post-menopausal females (OR = 1.06 (95% CI: 0.77–1.45), $P=0.73$) (**Figure 4**).

Degree of progression. To assess the impact of obesity on polyp progression, we calculated the OR of advanced adenoma compared with non-advanced adenoma. We identified nine studies (19,22, 23,27,28,36,38,39,41) reporting the prevalence of non-advanced and advanced adenoma according to BMI≥25 and BMI < 25. Although there was large heterogeneity between included studies ($I^2=55.8\%$), publication bias was not identified (Egger's test; bias = 0.96, $P=0.34$, Begg's test; Kendall's tau = −0.28, $P=0.36$). Two definitions of adenoma advancement were utilized. In seven studies, advanced adenoma was defined as cancer or adenoma measuring > 10 mm in diameter and/or villous component and/or showing severe dysplasia. In three studies, it was defined as adenoma measuring > 10 mm (38,40,41). We estimated pooled OR using all these studies, indicating obesity had no significant influence on adenoma progression (OR = 1.11 (95% CI: 0.90–1.36), $P=0.33$) (**Figure 5**). Subgroup analyses by definitions of advanced adenoma demonstrated similar ORs.

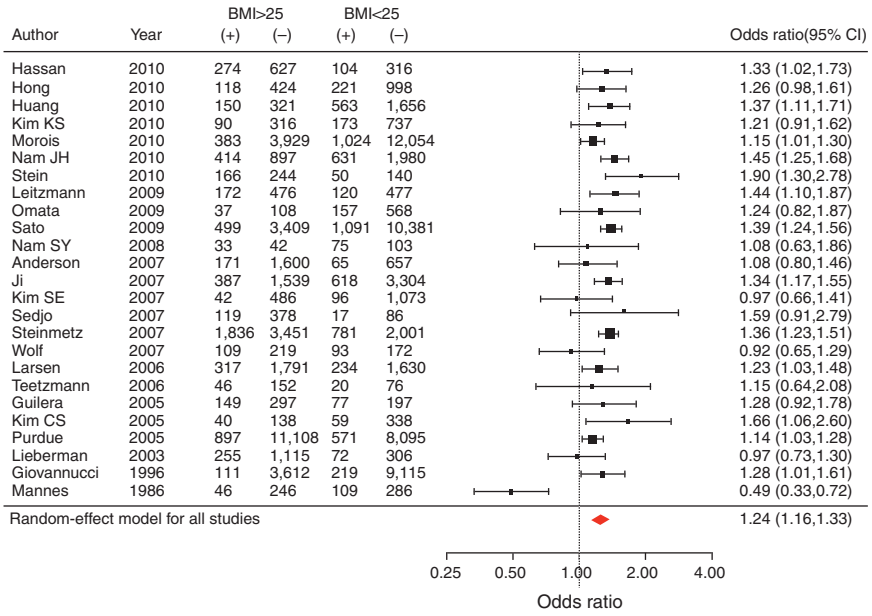

Figure 2. Forest plot of odds ratios of colorectal adenomas. Squares and horizontal bars represent within-trial odds ratios and 95% CIs, respectively, on a log scale. The size of squares represents study weight. Diamonds represent pooled odds ratios and 95% CIs, adjusted for source trial. BMI, body mass index; CI, confidence interval.

Meta-regression. We explored covariates affecting heterogeneity of ORs among included studies. Univariate meta-regression analysis identified year of publication (coefficient = 0.027 (95% CI: 0.013–0.040), $P<0.001$) and percentage of current smoking (coefficient = 0.005 (95% CI: 0.001–0.008), $P=0.007$) as a significant source of heterogeneity (**Table 3**). Furthermore, the percentage of family history was also shown to have a marginally significant effect as source of heterogeneity (coefficient = −0.013 (95% CI: −0.027 to 0.001), $P=0.066$). Multivariate meta-regression analysis did not identify any covariate as independent source of heterogeneity.

Dose–response relationship of BMI increment to colorectal adenoma. Direct comparison analysis demonstrated the OR of colorectal adenoma between BMI categories, including BMI < 25, 25–30, ≥30 to increase significantly with progressively higher BMIs to follow a dose–response relationship (BMI 25–30 vs. BMI < 25; OR = 1.21 (95% CI: 1.08–1.36), $P<0.01$, BMI≥30; OR = 1.33 (95% CI: 1.19–1.47), $P<0.01$). Twelve studies reported on the prevalence of colorectal adenoma according to these BMI categories (18,20,28,30,32,36–42). Multivariate meta-analysis was used as part of sensitivity analysis to assess the robustness of this dose–response relationship. Unadjusted multivariate meta-analysis supported our direct comparison results to reveal a positive correlation between higher BMI categories and the prevalence of colorectal adenoma (BMI 25–30 vs. BMI < 25; OR = 1.21 (95% CI: 1.07–1.38), $P<0.01$; BMI≥30 vs. BMI < 25; OR = 1.32 (95% CI: 1.18–1.48), $P<0.01$) (**Table 4**). Multivariate meta-regression analysis adjusted for a single covariates demonstrated that the percentage of family history may be significant source of heterogeneity (BMI 25–30, $P=0.01$; BMI≥30, $P=0.08$) (**Table 5**). Adjusted multivariate meta-regression analysis found no covariant as a source of heterogeneity, and also no statistical significance was identified with regards to the influence of obesity on the prevalence of colorectal adenoma although only seven studies were analyzed (**Table 4**).

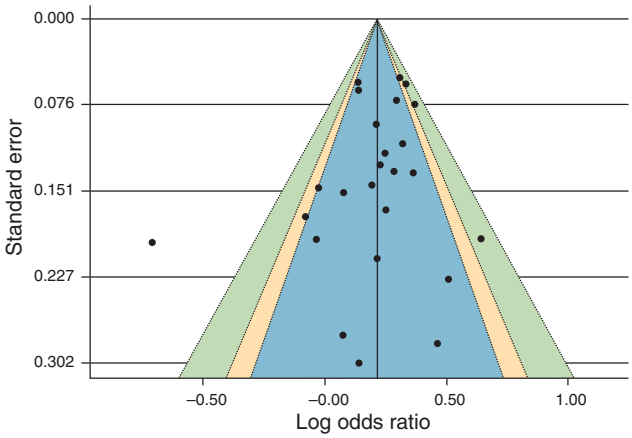

Figure 3. Funnel plot. The tests for funnel plot asymmetry by Egger's test and Begg's test identified no publication bias (Egger's test; bias = −1.08, $P=0.28$, Begg's test; Kendall's tau = −0.14, $P=0.37$).

DISCUSSION

Our results reveal that the overweight and obese population demonstrates an increased risk of colorectal adenoma prevalence by 24%. The positive association between BMI and adenoma

prevalence follows a dose–response relationship. This effect is consistent in the majority studies in our analysis and identifies excess weight as an expected but novel predictor of colorectal adenoma formation. Our findings reveal that adiposity may carry a larger impact on tumor initiation and adenoma formation with possibly less contribution to subsequent acceleration and growth from adenoma to carcinoma. The moderate heterogeneity from our data, however, requires caution when interpreting the results. Our meta-regression analysis also suggested that active smoking may be significantly associated with colorectal adenoma prevalence. The results of this meta-analysis reinforce the value of colorectal adenoma and polyp screening in overweight and obese patients at colonoscopy.

There is increasing epidemiological and meta-analytical evidence associating raised BMI and obesity with several cancers including CRC (8,43–51). One analysis from 29 CRC data sets, including 67,361 incident cases, demonstrated that higher BMI was associated with an increased risk of colon and rectal cancers (8). Our novel finding that obesity is positively associated with the risk of adenoma prevalence suggests that the tumorigenic effect of obesity is not only limited to colonic polyps and adenocarcinomas, but may also have a role earlier in the progression from epithelium to adenoma and subsequently carcinoma according to the Fearon and Vogelstein's model (52) for CRC development.

The present findings seem to be consistent with a recent meta-analysis on BMI and colorectal adenoma risk (53). The authors demonstrated a positive correlation between BMI and the prevalence of colorectal adenomas; however, we note several differences between this study and our analysis. These include: (i) statistical methodology, (ii) inclusion criteria of relevant studies, and (iii) assessment for risk of bias. Ben *et al.* (53) utilized the variance-weighted least squares regression analysis to confirm the dose–response relationship between obesity and outcomes of interest. This method requires the assumption of linearity in terms of the dose–response relationship between obesity and the outcomes of interest. However, this assumption was violated in two of the included studies (18,42). It has been shown that the association between BMI and outcomes of interest such as cancer-related mortality and post-operative complications typically follow a U- or J-shaped pattern (54,55). To accommodate for this association, we applied multivariate meta-analysis to assess for a dose–response relationship between BMI category and adenoma prevalence, where the linearity assumption is not required. Second, with regard to study design, the inclusion of cross-sectional databases is preferable for examining prevalence as the inclusion of case–control studies may introduce selection bias into the analysis. To avoid this risk of bias, we excluded case–control studies in our meta-analysis, whereas Ben *et al.* did not. Finally, given the presence of large heterogeneity in both our study and the manuscript of Ben *et al.*, the assessment for risk of bias and

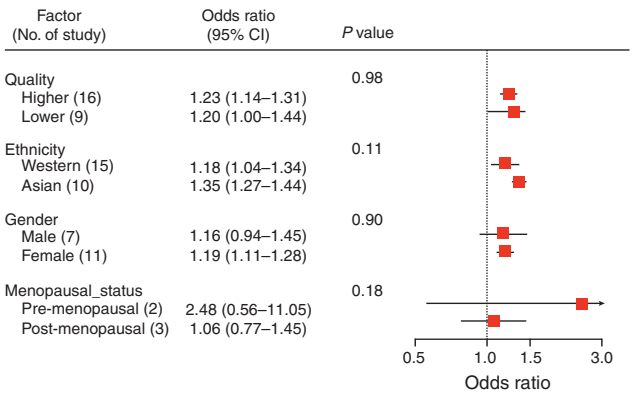

Figure 4. Forest plot of odds ratios of colorectal adenomas for subgroups. CI, confidence interval.

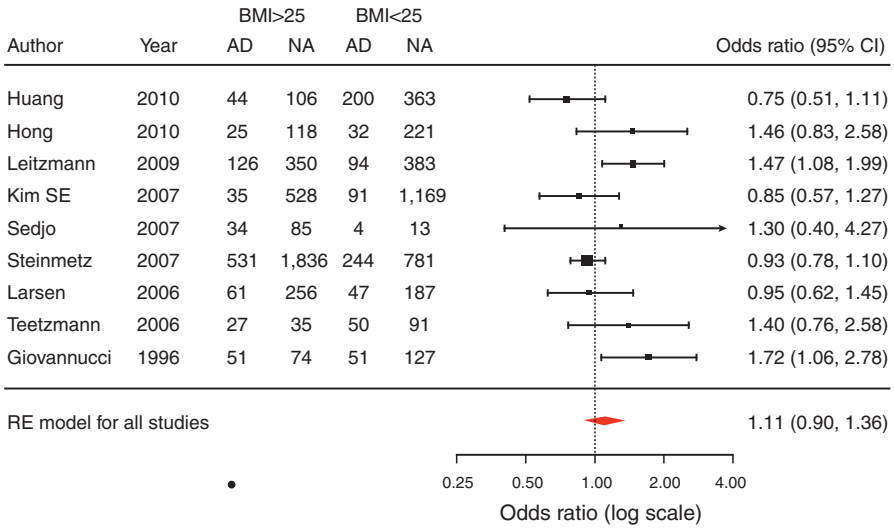

Figure 5. Forest plot for risk of adenoma progression. There is no significant difference between BMI≥25 and BMI<25 in adenoma progression. AD, advanced adenoma; BMI, body mass index; NA, non-advanced adenoma; CI, confidence interval; RE, random effect.

Table 3. Univariate and multivariate meta-regression analysis

Factor (number of studies)	Univariate		Multivariate	
	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Year of publication (25)	0.027 (0.013–0.040)	<0.001	0.020 (−0.008 to 0.049)	0.1663
Prospective study (25)	−0.093 (−0.256 to 0.070)	0.265		
Study reporting only AD (25)	0.017 (−0.190 to 0.224)	0.870		
Asian ethnicity (25)	0.106 (−0.025 to 0.237)	0.113		
Sample size (>1,000) (25)	0.088 (−0.092 to 0.267)	0.338		
Average age (17)	0.000 (−0.025 to 0.024)	0.975		
Female[a] (23)	0.000 (−0.003 to 0.003)	0.800		
Current smoking[a] (16)	**0.005 (0.001–0.008)**	**0.007**	0.003 (−0.004 to 0.011)	0.3915
Current drinking[a] (10)	0.000 (−0.003 to 0.004)	0.927		
Family history[a] (12)	−0.013 (−0.027 to 0.001)	0.066	−0.012 (−0.025 to 0.001)	0.0664
Methods of diagnosis[a] (25)	0.007 (−0.002 to 0.015)	0.108		
Obese cohort (≥30%) (12)	−0.006 (−0.023 to 0.011)	0.486		
Total colonoscopy (25)	0.033 (−0.128 to 0.195)	0.685		

AD, adenoma; CI, confidence interval.
[a]Percentage in cohorts, obese cohort; study including obese patients >30% of cohort.
Values in bold indicate significant difference.

Table 4. The estimated odds ratio for colorectal adenoma formations in patients with BMI 25–30 and ≥30 by univariate and multivariate meta-analysis, compared with those with BMI<25

Comparison	Unadjusted (12 studies)			Adjusted by covariates[a] (7 studies)		
	OR (95% CI)	*P* value	I^2	OR (95% CI)	*P* value	I^2
BMI<25 vs. 25–30	1.21 (1.07–1.38)	<0.01	67	1.29 (0.78–2.14)	0.32	48
BMI<25 vs. ≥30	1.32 (1.18–1.48)	<0.01	21	1.40 (0.87–2.24)	0.16	6

OR, odds ratio; CI, confidence interval.
[a]Adjusted for year of publication, the percentage of family history and obese cohort (obesity≥30%).

its influence on outcomes is essential to better understand the robustness of the available evidence. Although Ben *et al.* did not undertake any risk of bias assessment, we considered this as part of our study.

The effects of gender demonstrate paradoxical effects when comparing the BMI–CRC association with the BMI–colorectal adenoma association. Men have been shown to have a higher association with BMI and CRC (56), although the findings of this meta-analysis did not demonstrate any significance of male gender on colorectal adenoma formation in relation to BMI. Conversely, our study did reveal a significant association between female gender and colorectal adenoma formation according to BMI. This is a new finding, although the mechanisms linking gender and obesity on adenoma formation have not been fully established. One possible explanation for this association may include the role of endogenous and exogenous sex hormones on the adenocarcinoma sequence. As presented in **Figure 4**, pre-menopausal females demonstrated a stronger susceptibility to colorectal adenoma formation, although this association disappeared for post-menopausal females. This may indicate that endogenous estrogens might have an important role in colorectal adenoma formation. This is supported by mechanistic studies demonstrating an increase in gene transcription and cancer proliferation following the activation of estrogen receptor-α (57). In contrast, several studies reveal exogenous estrogens to offer a protective effect on colorectal neoplasm formation (56). As a result, further mechanistic studies of colorectal adenoma initiation and progression are required to better understand the association between obesity and gender on adenoma formation. Additionally, our results demonstrated that current smoking might increase the risk of colorectal adenoma prevalence, suggesting that smoking may have a role in adenoma formation. This is supported by large-scale studies identifying smoking status as risk a factor for colorectal adenoma and cancer prevalence (58,59).

Table 5. Multivariate meta-regression analysis

Factor (number of studies)	Unadjusted (12 studies)				Adjusted by covariates[a] (7 studies)			
	BMI<25 vs. BMI 25–30		BMI<25 vs. BMI 30		BMI<25 vs. BMI 25–30		BMI<25 vs. BMI 30	
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*
Year of publication (12)	0.050 (−0.006 to 0.106)	0.080	0.037 (−0.010 to 0.083)	0.125	0.052 (−0.014 to 0.118)	0.120	0.043 (−0.012 to 0.098)	0.128
Prospective study (12)	−0.193 (−0.586 to 0.201)	0.337	0.110 (−0.199 to 0.420)	0.485				
Study reporting only AD (12)	0.152 (−0.187 to 0.491)	0.380	−0.012 (−0.311 to 0.286)	0.935				
Asia (12)	0.223 (−0.158 to 0.605)	0.252	−0.107 (−0.594 to 0.381)	0.668				
Sample size (>1000) (12)	0.001 (−0.305 to 0.307)	0.994	−0.150 (−0.404 to 0.103)	0.244				
Average age (14)	−0.011 (−0.042 to 0.019)	0.471	−0.007 (−0.039 to 0.025)	0.664				
Female[a] (12)	0.000 (−0.005 to 0.005)	0.915	0.002 (−0.002 to 0.005)	0.401				
Current smoking[a] (10)	0.010 (−0.002 to 0.023)	0.101	−0.002 (−0.012 to 0.008)	0.756				
Current drinking[a] (5)	0.009 (−0.008 to 0.025)	0.291	−0.003 (−0.016 to 0.010)	0.662				
Family history[a] (7)	**−0.029 (−0.053 to 0.006)**	**0.014**	−0.023 (−0.049 to 0.003)	0.077	−0.021 (−0.046 to 0.005)	0.108	−0.015 (−0.040 to 0.010)	0.247
Methods of diagnosis[a] (12)	0.229 (−0.086 to 0.543)	0.154	0.085 (−0.238 to 0.409)	0.606				
Obese cohort (≥30%) (11)	0.052 (−0.334 to 0.437)	0.793	0.289 (−0.009 to 0.586)	0.057	−0.028 (−0.381 to 0.326)	0.878	0.175 (−0.147 to 0.497)	0.287
Total colonoscopy								

AD, adenoma; BMI, body mass index; CI, confidence interval.
[a]Percentage in cohorts, obese cohort; study including obese patients >30% of cohort.
Values in bold indicate significant difference.

For most clinical studies, head-to-head comparisons have traditionally been considered to be the most appropriate method of answering clinical questions. However, studies exploring the impact of obesity on systemic diseases are unsuitable for statistically robust head-to head comparisons due to a lack of prospective comparative studies and the skewed distribution of body weight and BMI in obese and overweight patients. We therefore applied multivariate meta-analysis in our study to provide more precise estimates of effect size of multiple outcomes when compared with statistical analyses based on direct evidence alone (60). We utilized this method for all our study cohorts to better understand the correlation between obesity and adenoma formation despite the possible statistical limitation of study design. We only included studies with consecutive data to minimize variability between included data sets. Consequently, we demonstrated that multivariate meta-analysis using observational trials can provide appropriate statistical results under controlled situations.

We also demonstrated that an increased percentage of CRC family history might be negatively correlated with colorectal adenoma prevalence. This may indicate that the paradoxical effects of obesity on colorectal adenoma formation in patients with an already established genetic tumorigenic environment. Hereditary non-polyposis CRC is a hereditary CRC type that is observed in 15–20% of sporadic CRCs. Hereditary non-polyposis CRC is frequently associated with microsatellite instability induced by germ-line mutations of the mismatch repair genes, including *MLH1*, *MLH2*, *MSH3*, *MSH6*, *PMS1*, and *PMS2* (61,62). It has been demonstrated that BMI is positively associated with stable and low microsatellite instability status but not with high microsatellite instability tumors (63). These results suggest that obesity may have less influence on the incidence of hereditary CRC compared with that of non-hereditary CRC. Despite these findings, the effects of family history on CRC are not entirely clear. Therefore, the effects of obesity on CRCs of different genotypes and heredities require further mechanistic

investigations utilizing robust genetic and molecular analyses in larger patient populations.

There were some limitations in this review. There was a heterogeneity deriving from the assessment of prevalence based on self-assessed questionnaires and no fixed protocol for colonoscopy was identified. Assessments utilizing self-report methods can be subject to recall bias. Obesity is also an independent predictor of inadequate bowel preparation at colonoscopy (64) so that the prevalence of adenoma in obese patients may be underestimated. Moreover, there may have been an inconsistency in the awareness and identification of colorectal adenomas between studies. This would have been dependent on the skill and expertise of endoscopists at each study center. Another limitation was the heterogeneity between timing and method of adenoma evaluation, particularly as there is an increasing risk of developing spontaneous adenoma over time. Furthermore, we were unable to assess the protective effects of weight reduction on adenoma formation due to a lack of studies (35). Weight gain of >4 pounds was associated with an ~2-fold increase in advanced and non-advanced adenomas (36). At the second colonoscopy after 1 year, the incidence rates of colorectal adenoma were 9.3% (14/150) in the weight-reduction group, 16.2% (19/117) in the weight-gain group, and 17.1% (394/2,301) in the no-change group, in which the OR by weight reduction adjusted for sex, age, initial tumor number and size, and initial BMI was estimated 0.47 (95% CI = 0.26–0.83, $P = 0.01$) (65).

The mechanisms of colorectal tumorigenesis and progression associated with obesity are unclear. Our findings reveal that obesity may carry a larger impact on tumor initiation and adenoma formation with possibly less contribution to subsequent acceleration and growth from adenoma to carcinoma. This is because we demonstrated a significant association between obesity and the relative risk of adenoma prevalence, although obesity had no significant influence on the relative risk of adenoma progression. The mechanisms linking obesity with colorectal adenomas and cancers include genetic alterations such as the common single-nucleotide polymorphism variants around the melanocortin 4 receptor gene, which is associated with both obesity and colorectal neoplasms (66). The contribution of excess weight to the various steps of the Fearon and Vogelstein model of CRC initiation and progression has not yet been studied in-depth so that further identification of the tumorigenic effects of adiposity in cancer progression may lead to novel interventions in cancer management.

In conclusion, the positive association between obesity and colorectal adenoma prevalence demonstrates an underlying dose–response relationship according to BMI. This effect is consistent in the majority studies in our analysis and identifies excess weight as an expected but novel predictor of colorectal adenoma formation. Our findings reveal that adiposity may carry a larger impact on tumor initiation and adenoma formation with possibly less contribution to subsequent acceleration and growth from adenoma to carcinoma. The timely screening of overweight and obese patients for colorectal adenomas should be performed with careful consideration of the influence of epidemiologic data (gender, active smoking, family history of CRC, and diagnostic procedures for adenomas).

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CONFLICT OF INTEREST

Guarantor of the article: Thanos Athanasiou, MD, PhD, FRCS, FETCS.

Specific author contributions: Conceived and drafted the study, analyzed and interpreted data, and drafted the manuscript: Koji Okabayashi, Hutan Ashrafian, and Thanos Athanasiou; collected all data: Koji Okabayashi and Hutan Ashrafian; ; all authors commented on drafts of the paper; all authors have approved the final draft of the manuscript.

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