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Anthropometric factors and endometrial cancer risk: A systematic review and dose-response meta-analysis of prospective studies

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Summary

Background: Greater body mass index has been convincingly related to increased endometrial cancer risk, however, whether adiposity earlier in life or abdominal fatness, is an independent risk factor and whether weight gain or greater height increases the risk is not clear.

Methods: As part of the Continuous Update Project of the World Cancer Research Fund International we conducted a systematic review and meta-analysis of prospective studies of the association between anthropometric measures and endometrial cancer risk and searched PubMed and several other databases up to February 2015. Summary relative risks were calculated using a random effects model.

Results: Thirty prospective studies of BMI and endometrial cancer risk with 22320 cases among 6445402 participants were included. The summary relative risk (RR) for a 5 unit increment was 1.54 (95% CI: 1.47-1.61, I^2=81%). Although the test for nonlinearity was significant, $p_{nonlinearity}$<0.0001, and the curve was steeper within the overweight and obese BMI ranges, there was evidence of increased risk even within the high normal BMI range. The summary RR was 1.45 (95% CI: 1.28-1.64, I^2=76%) per 5 BMI units for BMI in young adulthood, 1.18 (95% CI: 1.14-1.23, I^2=67%) per 5 kg increase of weight, and 1.16 (95% CI: 1.12-1.20, I^2=51%) per 5 kg of weight gained between young adulthood and study baseline, 1.27 (95% CI: 1.17-1.39, I^2=71%) per 10 cm increase in waist circumference, 1.21 (95% CI: 1.13-1.29, I^2=0%) per 0.1 unit increment in waist-to-hip ratio and 1.30 (95% CI: 1.19-1.41, I^2=0%) per 10 cm increase in hips circumference. The summary RR was 1.15 (95% CI: 1.09-1.22, I^2=61%) for a 10 cm increase in height.

Conclusions: All measures of adiposity were associated with increased risk of endometrial cancer, and in addition increasing height was associated with increased risk.

Key words: Body mass index, waist circumference, waist-to-hip ratio, height, endometrial cancer, systematic review, meta-analysis.

Key message: Although there is strong evidence that general adiposity increases endometrial cancer risk, the evidence for an association between adiposity at younger ages, abdominal fatness, weight gain and greater height in relation to endometrial cancer risk is less substantial. This meta-analysis reinforces the importance of weight control in the prevention of endometrial cancer.

Introduction

Endometrial cancer is the 5th most common cancer among women with 320 000 new cases diagnosed in 2012 worldwide, accounting for 4.8% of all female cancer cases (1). The incidence of endometrial cancer has been increasing in populations undergoing urbanisation and economic growth, in parallel with increasing obesity rates and sedentary lifestyles (2;3).

Greater body fatness as measured by body mass index (BMI=kg of weight/height in metres^2) has been associated with increased risk of endometrial cancer in a large number of studies (4-13). In the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report from 2007 it was stated that the evidence that greater body fatness increases endometrial cancer risk was convincing (14). However, it is unclear whether greater BMI in early adulthood is more strongly associated with endometrial cancer, than BMI in mid-life and whether an association between early adulthood BMI is independent of mid-life BMI. In addition, greater abdominal fatness as measured by waist-to-hip ratio or waist circumference was probably associated with increased risk, but the few prospective studies available at that time limited the strength of the conclusions (14). Whether or not abdominal adiposity and overall adiposity independently of each other are associated with increased risk is also not known. In addition, several studies have assessed the association between weight changes between early adulthood and middle age in relation to endometrial cancer risk and these studies have indicated an increased risk with greater weight gain. If specific adiposity-related variables are more strongly associated with endometrial cancer than others it could provide more detailed and improved recommendations for endometrial cancer prevention as well as possible insights into underlying biological mechanisms. Relatively few studies had assessed height in relation to endometrial cancer at that time (5;8;15;16) and the evidence was considered limited, but suggestive of an increased endometrial cancer risk with greater height (14). A number of additional large cohort studies have been published on body fatness (17-31)

and height (20;31-35) in relation to endometrial cancer risk since the WCRF/AICR report and here we conducted an updated meta-analysis of the published studies as part of the WCRF International Continuous Update Project (CUP).

Methods

Search strategy

Initially relevant studies of anthropometric measures and endometrial cancer risk were identified by searching several databases up to December 2005, including Pubmed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, LILACS, Cochrane library, CINAHL, AMED, National Research Register, and In Process Medline. However, because all the relevant studies were identified by the PubMed search, a change to the protocol was made and in the updated searches only Pubmed was searched from 1st January 2006 to 26th of February 2015. The full search can be found in the supplement (Annex 1). A prespecified protocol was followed for the review (http://www.wcrf.org/sites/default/files/protocol_endometrial_and_ovarian_cancer.pdf) and we used standard criteria for meta-analyses of observational studies (36). In addition, we also searched the reference lists of all the studies that were included in the analysis and the reference lists of published meta-analyses (37;38).

Study selection

Published prospective or retrospective cohort studies, case-cohort studies, or nested case-control studies of the association between anthropometric measures and endometrial cancer risk were included in this review. Furthermore, to be eligible for inclusion manuscripts had to show relative risk estimates (hazard ratio, risk ratio, odds ratio) and 95% confidence

intervals and for the dose-response analysis, a quantitative measure of the exposure and the total number of cases and person-years. If there were several publications from the same study we used the study with the largest number of cases, or the study which provided sufficient detail of data to be included in dose-response analyses. A few duplicate publications reported on different exposures in each publication and then, both publications were used, but each study was only included once in the analysis of each exposure. We identified 43 publications (32 studies) that could be included in the analysis (4-13;15;17-24;26-35;39-52). A list of 31 publications that were excluded and exclusion reasons is found in Supplementary Table 1.

Data extraction

We extracted from each study: The first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, gender, age, number of cases, assessment method of anthropometric factors (measured vs. self-reported), type of anthropometric measure, RRs and 95% CIs, and variables adjusted for in the analysis. Reviewers at the Rutgers Cancer Institute of New Jersey conducted the search and data extraction of articles published up to December 2005, during the systematic literature review for the WCRF/AICR report (14). The search and data extraction from January 2006 and up to December 2013 was conducted by one author (DANR) and was checked for accuracy by two authors (TN, DA).

Statistical analysis

Summary RRs and 95% CIs for a 5 unit increment in BMI (kg/m^2), 5 kg increase in weight and weight gain, 10 cm increment in waist or hips circumference, 0.1 unit increment in waist-to-hip ratio and for a 10 cm increase in height were estimated using a random effects model (53). The average of the natural logarithm of the RRs was estimated and the RR from each

study was weighted by the inverse of its variance. A two-tailed $p<0.05$ was considered statistically significant. If studies reported results separately by menopausal status we combined the estimates using a fixed-effects model to generate an overall estimate, but the menopausal specific estimates were used as provided in subgroup analyses by menopausal status.

The method described by Greenland and Longnecker (54) was used for the dose–response analysis and study-specific slopes (linear trends) and 95% CIs were computed from the natural logs of the RRs and CIs across categories of anthropometric measures. The method requires that the distribution of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases or person-years in studies that did not report these, but reported the total number of cases and person-years (55). The mean BMI, waist circumference of waist-to-hip ratio level in each category was assigned to the corresponding relative risk for each study and for studies that reported these measures by ranges we estimated the mean in each category using the method described by Chene and Thompson (56). For studies which did not use the lowest category as the reference category we converted the risk estimates so that the lowest category became the reference category using the method by Hamling (57). A potential nonlinear dose-response relationship between BMI, waist circumference and waist-to-hip ratio and endometrial cancer was examined by using fractional polynomial models (58). We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity (58).

Subgroup and meta-regression analyses were conducted to investigate potential sources of heterogeneity and heterogeneity between studies was quantitatively assessed by the Q test and I^2 (59). Study quality was assessed using the Newcastle-Ottawa scale (60). Small

study effects, such as publication bias, were assessed by inspecting the funnel plots for asymmetry and with Egger's test (61) and Begg's test (62), with the results considered to indicate small study effects when $p<0.10$. Sensitivity analyses excluding one study at a time were conducted to clarify whether the results were simply due to one large study or a study with an extreme result.

Results

We identified 32 prospective studies (41 publications) that were included in the analyses of anthropometric factors and endometrial cancer risk (Supplementary Table 2 and 3). Characteristics of the included studies are provided in Supplementary Table 2 and Supplementary Table 3. Fifteen studies were from Europe, thirteen studies were from the North America, and four were from Asia. Anthropometric factors were measured in 14 studies and self-reported in 18 studies (Supplementary Table 2 and Supplementary Table 3) and were all assessed at baseline with the exception of BMI in young adulthood (at ages 18-25) where BMI was retrospectively assessed and the analysis of weight gain (defined as the difference between weight at baseline and age 18-20 years) where weight at age 18-20 years was assessed retrospectively.

BMI

Thirty prospective studies (28 publications, 28 risk estimates) (4-13;17-24;26-31) were included in the overall dose-response analysis of BMI and endometrial cancer incidence and included a total of 22320 cases among 6445402 participants. The summary RR for a 5 unit increment in BMI was 1.54 (95% CI: 1.47-1.61), with high heterogeneity, I^2=81%, $p_{heterogeneity}$<0.0001 (Figure 1a). There was no evidence of small study effects with Egger's test, p=0.41, or with Begg's test, p=0.77 and when visually inspected the funnel plot showed no indication of asymmetry. For two studies (20;30) which provided additional adjustment for waist-to-hip ratio the summary RR per 5 BMI units was 1.28 (95% CI: 1.17-1.40, I^2=46%, $p_{heterogeneity}$=0.17). There was evidence that the association between BMI and endometrial cancer was somewhat nonlinear, $p_{nonlinearity}$<0.0001, with risk increasing more noticeably for BMI over 25 kg/m^2, however, some increase in risk was observed even within the normal BMI range (Figure 1b, Supplementary Table 4). There was significant heterogeneity when stratified by hormone replacement therapy use, with a stronger association among never users

(20;21;24;29;39;45) compared to ever users (20;21;24;29;45), with summary RRs of 1.65 (95% CI: 1.33-2.05) and 1.10 (95% CI: 1.06-1.14), $p_{heterogeneity}$=0.005), respectively (Table 1). There was also a slightly weaker association in studies with adjustment for alcohol and hypertension compared to studies without such adjustment, $p_{heterogeneity}$=0.04 and $p_{heterogeneity}$=0.01. There was a positive association for both premenopausal and postmenopausal women, which appeared to be slightly stronger among postmenopausal women, however there was no heterogeneity by menopausal status, $p_{heterogeneity}$=0.68 (Table 1). Analysing three studies that reported on endometrial cancer mortality (19;46;47) gave a summary RR of 1.45 (95% CI: 1.30-1.63, I^2=33%, $p_{heterogeneity}$=0.22) (Figure 2a), and there was evidence of nonlinearity in the analysis of endometrial cancer mortality as well, $p_{nonlinearity}$<0.0001 (Figure 2b, Supplementary Table 5).

BMI at age 18-25 years

Nine cohort studies (8;15;21;29;31;39;41;45;48) were included in the analysis of BMI at 18-25 years and included 4345 cases among 631915 participants. The summary RR per 5 units increase in BMI was 1.45 (95% CI: 1.28-1.64, I^2=76%, $p_{heterogeneity}$<0.0001, Figure 2c). The heterogeneity appeared to be explained by the Million Women Study (19) and the ARIC study (41) and when excluded, I^2=0%, $p_{heterogeneity}$=0.44 and the association was still significant, summary RR=1.30 (95% CI: 1.23-1.39). There was no evidence of publication bias with Egger's test, p=0.41 or with Begg's test, p=0.92. The test for nonlinearity was not significant, $p_{nonlinearity}$=0.09, and the association appeared to be approximately linear from a BMI of 20 kg/m^2 and above (Figure 2d, Supplementary Table 6). Restricting the analysis to three studies (21;39;45) which provided additional models with further adjustment for current BMI and which could be included in a dose-response analysis, attenuated the association and it was no longer significant, summary RR=1.00 (95% CI: 0.92-1.08, I^2=0%, $p_{heterogeneity}$=0.43)

(none of the results which were used for the main analysis adjusted for current BMI). There was little evidence of heterogeneity between subgroups (Table 1).

Weight

Eight cohort studies (5;6;8;20;31;43;49;50) were included in the weight and endometrial cancer analysis and included 1841 cases among 343866 participants. The summary RR was 1.18 (95% CI: 1.14-1.23) per 5 kg and there was high heterogeneity, I^2=67%, $p_{heterogeneity}$=0.004 (Figure 3a). The EPIC study (20) explained much of the heterogeneity and when excluded, I^2=17%, $p_{heterogeneity}$=0.30 and the summary RR was 1.20 (95% CI: 1.16-1.24). There was no evidence of publication bias with Egger's test, p=0.16, or with Begg's test, p=0.54. There was evidence that the association between BMI and endometrial cancer was nonlinear, $p_{nonlinearity}$=0.0001, and the curve was steeper at higher levels of weight (Figure 3b, Supplementary Table 7). There was little evidence of heterogeneity between subgroups (Table 2).

Weight gain

Seven cohort studies (15;20;21;29;31;41;45) were included in the analysis of weight gain between age 18-20 and baseline and endometrial cancer risk and included 2806 cases among 460901 participants. The summary RR per 5 kg increase in weight gain was 1.16 (95% CI: 1.12-1.20) with high heterogeneity, I^2=51%, $p_{heterogeneity}$=0.06 (Figure 3c). When the analysis was restricted to four studies (15;21;41;45) with further adjustment for BMI or weight in young adulthood the results persisted, summary RR=1.18 (95% CI: 1.15-1.21, I^2=0%, p=0.58). Although the test for nonlinearity was significant, $p_{nonlinearity}$=0.003, the association was largely linear over most of the range, and was clearer for weight gain of over

10 kg (Figure 3d, Supplementary Table 8). There was no evidence of heterogeneity between subgroups in stratified analyses (Table 2).

Waist circumference

Four cohort studies (20;28;29;51) were included in the analysis of waist circumference and endometrial cancer risk and included 1524 cases among 315770 participants. The summary RR for a 10 cm increase in waist circumference was 1.27 (95% CI: 1.17-1.39) with high heterogeneity, I^2=70%, p=0.02 (Figure 4a). For two studies which further adjusted for BMI as exploratory analyses (20;28), the summary RR was 1.26 (95% CI: 1.18-1.34, I^2=70%, $p_{heterogeneity}$=0.38). There was evidence of a nonlinear association between waist circumference and endometrial cancer risk, $p_{nonlinearity}$<0.0001, with a steeper increase in risk at higher levels of waist circumference (Figure 4b, Supplementary Table 9).

Waist-to-hip ratio

Five cohort studies (7;20;28-30) were included in the analysis of waist-to-hip ratio and endometrial cancer risk and included 2447 cases among 394340 participants. The summary RR for a 0.1 unit increment in waist-to-hip ratio was 1.21 (95% CI: 1.13-1.29) with no significant heterogeneity I^2=0%, $p_{heterogeneity}$=0.48 (Figure 4c). For three studies with further adjustment for BMI (20;28;30), the summary RR was 1.07 (95% CI: 0.97-1.17, I^2=0%, $p_{heterogeneity}$=0.48). There was no evidence of a nonlinear association between waist-to-hip ratio and endometrial cancer risk, $p_{nonlinearity}$=0.29 (Figure 4d, Supplementary Table 10).

Hips circumference

Only two studies were included in the analysis of hip circumference (20;28) and included 831 cases among 255650 participants. The summary RR per 10 cm increase in hip circumference was 1.30 (95% CI: 1.19-1.41, I^2=0, $p_{heterogeneity}$=0.34) (Figure 5).

Height

We identified thirteen cohort studies (12 publications, 12 risk estimates) (5;8;17;20;22;31-35;43;52) that could be included in the analysis of height and endometrial cancer risk and included 20519 cases among 3453714 participants. The summary RR per 10 cm increase in height was 1.15 (95% CI: 1.09-1.22, I^2=61%, $p_{heterogeneity}$=0.003) (Figure 6a). There was no evidence of publication bias with Egger's test, p=0.61 or with Begg's test, p=0.54. There was no evidence of a nonlinear association between height and endometrial cancer, $p_{nonlinearity}$=0.39 (Figure 6b, Supplementary Table 11). There was little evidence of heterogeneity in subgroup analyses (Table 2).

Study quality and sensitivity analyses

There was no evidence that the results differed when stratified by study quality scores, and in general the study quality was high (Table 1, Table 2). For example mean (median) study quality scores were 7.5 (8.0) for the analysis of BMI, 6.9 (7.0) for BMI in young adulthood, 7.0 (7.5) for weight, 7.3 (7.0) for weight gain, and 7.8 (8.0) for height, out of a maximum of 9 points. When excluding one study at a time none of the associations were materially altered (Supplementary text).

Discussion

In this meta-analysis we found evidence of an increased risk of endometrial cancer with higher BMI, BMI at ages 18-25, weight, weight changes (weight gain), waist circumference, hip circumference, waist-to-hip ratio, and height (Supplementary Table 12). The summary estimate from the current analysis (1.54 (95% CI: 1.47-1.61, n=28) is consistent with those from previous meta-analyses (1.59, 95% CI: 1.50-1.68, n=19, for the analysis by Renehan et al, and 1.60, 95% CI: 1.52-1.68, n=24, for the analysis by Crosbie et al) which also found strong increases in the risk of endometrial cancer risk with greater body mass index (37;38). However, to our knowledge this is the first meta-analysis to comprehensively assess several anthropometric measures including BMI in young adulthood, weight, weight changes, and abdominal measures of adiposity, to examine and quantify the independent effect of abdominal and overall adiposity, and to examine the shape of the dose-response relationship between different measures of body fatness and endometrial cancer. Our results consistently show a dose-response association of increasing risk with greater body fatness, and there appeared to be an independent association of BMI and waist circumference with endometrial cancer risk. Both BMI in young adulthood and weight gain between early adulthood and middle age was positively associated with endometrial cancer risk, the latter being consistent with a recent meta-analysis (63). There was evidence of a nonlinear association in most of the analyses, and the increased risk appeared to be steeper at higher levels of exposure for BMI (>25 kg/m^2), weight (>65-70 kg) and waist circumference (>85 cm), while for BMI at ages 18-25, weight changes, and waist-to-hip ratio, as well as the analysis of BMI and endometrial cancer mortality the associations appeared to be linear above a certain point. However, there was evidence of increased endometrial cancer risk with increasing BMI even within the normal BMI range suggesting that relatively lean women (BMI around 20) have the lowest risk.

Several potential mechanisms may explain an association between greater adiposity and increased endometrial cancer risk. Excess weight influences both the synthesis and bioavailability of sex steroids through several biologic pathways. Adipose tissue expresses sex-steroid metabolizing enzymes which convert androgenic precursors, secreted by the gonads and adrenal glands, to estrogens. After the menopause, adipose tissue becomes the main site of estrogen synthesis through the aromatization of adrenal androgens. Greater overall and abdominal adiposity after menopause increases levels of insulin and insulin-like growth factor 1 (IGF-1) (64), which reduces hepathic synthesis and blood concentrations of sex hormone-binding globulin (65;66), and leads to higher levels of free estrogens (64). BMI is related to a linear increase in serum concentrations of estrogens (67), which in turn increases endometrial cancer risk (68). Greater concentrations of sex-hormone-binding globulin has been associated with reduced risk of endometrial cancer (68). The association between BMI and endometrial cancer was positive in both premenopausal and postmenopausal women, and although the test for heterogeneity by menopausal status was not significant, the association appeared to the slightly stronger among postmenopausal women, which is consistent with these mechanisms. In an analysis from the EPIC-study the association between BMI and endometrial cancer was reduced from 2.67 (95% CI: 1.63-4.37) to 2.09 (95% CI: 1.22-3.57) for BMI ≥30 vs. 25 when adjusted for free estradiol, suggesting that part of the association between BMI and endometrial cancer may be mediated by increased estradiol levels (68). Adiposity is also associated with insulin resistance and increased risk of type 2 diabetes (69). Type 2 diabetes is an established risk factor for endometrial cancer (70), and there is suggestive evidence that risk increases even in the prediabetic state (71-73) and with elevated insulin and/or C-peptide concentrations (74;75), suggesting a potential role of insulin resistance and/or hyperinsulinemia. Further support for

this hypothesis comes from a meta-analysis which showed increased endometrial cancer risk among women with the metabolic syndrome (76).

There was evidence of effect modification by hormone replacement therapy use, which is an independent risk factor for endometrial cancer (77), and the association was much stronger in never users than in ever users. This finding is expected, as circulating estrogens is a major factor in the relationship between body fatness and endometrial cancer (64;68). Because circulating estrogen levels are mainly determined by the exogenous hormones in hormone therapy users, the potential for overweight and obesity to increase circulating estrogens and endometrial cancer risk is relatively smaller in hormone therapy users than in non-users.

To our knowledge this is the first meta-analysis of prospective studies to report a significantly increased risk of endometrial cancer with greater height. In the WCRF/AICR 2007 report there was only limited and suggestive evidence for an association between height and endometrial cancer risk (14), but in the current analysis six additional publications were included and this provided statistical power to detect an association. Although there is strong evidence for an association between greater height and increased risk of other cancers including cancers of the breast, colorectum, pancreas, and ovaries (14;78), the specific mechanism that may explain an association between greater height and endometrial cancer risk is not clear. Elevated levels of insulin-like growth factor-1 (IGF-1) has been implicated in other cancers as it is an important determinant for growth and may inhibit apoptosis, stimulate cell proliferation and synthesis of sex steroids and inhibit the synthesis of SHBG (79). However, epidemiological data relating IGF-1 to endometrial cancer risk have not been consistent (80;81), although a few studies suggested a positive association with IGF-2 (82;83).

Our meta-analysis has some limitations which may affect the interpretation of the results. Although there was high heterogeneity in most of the adiposity-related analyses this appeared to be attributable to differences in the strength of the association, rather than on differences in the directionality of effect as all studies apart from one reported risk estimates in the direction of increased risk. The positive associations observed persisted among almost all subgroup analyses. Another limitation is the low to moderate number of cohort studies available reporting on waist circumference, hip circumference and waist-to-hip ratio which limited our possibility to conduct subgroup analyses and test for publication bias for these measures. Although our analysis suggest that both high BMI and waist circumference increase endometrial cancer risk, few studies have conducted further adjustments between BMI and waist measures to try to clarify their independent role. This is a limitation and therefore needs further assessment in any future studies. In addition, further analyses of waist measures within strata of BMI (and vice versa) could clarify potential gains by using additional adiposity measures. It is not surprising that the association between BMI in young adulthood and endometrial cancer was attenuated among three studies which further adjusted for baseline BMI, because adiposity in early adulthood is highly correlated with adiposity in middle age (84-88). The positive association between early adulthood BMI and endometrial cancer may therefore largely be mediated through a greater body size later in life. There were fewer studies in the analysis of height than in the analysis of BMI, and it is unclear whether this is due to selective publication bias or if the data were not analysed due to the lack of a previous hypothesis. Although it is possible that confounding may have affected the results as overweight and obese women usually are less physically active and have unhealthier diets than normal weight women, it is unlikely that such confounding could entirely explain the association because the risk associated with body fatness is much stronger than those observed for both physical activity and dietary factors. In addition, the results persisted in

subgroup analyses by adjustment for confounding factors and there was little evidence of heterogeneity between these subgroups. Lastly, there were too few studies to analyse the two subtypes of endometrial cancer (type 1 and type 2) separately, but the few available cohorts (17;89) and a pooled analysis of cohorts and case-control studies (90) found increased risk for both types, although the association was stronger for type 1 than for type 2 cancers.

Measurement errors in the assessment of height and weight may have influenced our results. Most of the studies relied on self-reported height and weight, however, there is generally a high correlation between self-reported and measured height and weight (91). There was heterogeneity in the subgroup analysis of weight by whether or not the exposure was measured or self-reported, with a weaker, but still significant association in the studies with measured weight compared to those with self-reported weight. However, there was no heterogeneity in the association between BMI and endometrial cancer when stratified by the exposure assessment. Although meta-analyses of published literature may be susceptible to publication bias, we found no evidence of publication bias with either Egger's test or with Begg's test or when visually inspecting the funnel plots.

Our meta-analysis also has several strengths. Because we based our analysis on prospective studies, recall bias is not likely to explain our findings and there is less possibility for selection bias. In addition, weight loss among cases is less likely to have affected the results than in case-control studies. Our meta-analysis included a large number of cohort studies with relatively long follow-up and included >22300 cases among >6.4 million participants in the BMI analysis, so we had statistical power to detect even moderate associations. We also had statistical power to detect associations in several subgroup analyses, including by menopausal status and by use of hormone replacement therapy, and by adjustment for confounding factors. The results were robust to the influence of single studies and the study quality was high overall. The current findings reinforce the importance of

weight control for endometrial cancer prevention. Given the positive associations between both early adulthood BMI and weight gain from early adulthood to middle-age and endometrial cancer risk, as well as the strong correlation between early adulthood BMI and middle age BMI, efforts to prevent both excess weight and cancer should start earlier in life.

In summary, this meta-analysis confirms a positive association between body fatness, weight gain and height and endometrial cancer risk. Any further studies should further assess the association between abdominal obesity and weight changes and endometrial cancer risk. Our findings confirm the previous recommendations for women to be as lean as possible within the normal BMI range and suggest that avoiding excess weight gain between young adulthood and middle age may reduce the risk of endometrial cancer.

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Conflict of interest: The authors declare that there are no conflicts of interest.

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Table 1: Subgroup analyses of BMI and BMI in young adulthood and endometrial cancer

		BMI, per 5 units (kg/m^2)					**BMI in young adulthood, per 5 units (kg/m^2)**				
		n	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]	*n*	RR (95% CI)	I^2 (%)	P_h[1]	P_h[2]
All studies		28	1.54 (1.47-1.61)	80.9	<0.0001		9	1.45 (1.27-1.65)	74.3	<0.0001	
Duration of follow-up											
<10 yrs follow-up		13	1.53 (1.43-1.64)	79.5	<0.0001	0.88	4	1.46 (1.14-1.87)	88.0	<0.0001	0.91
≥10 yrs follow-up		15	1.55 (1.45-1.66)	83.0	<0.0001		5	1.40 (1.24-1.59)	35.2	0.19	
Assessment of weight/height											
Measured		13	1.48 (1.37-1.60)	83.4	<0.0001	0.16	0				NC
Self-reported		15	1.59 (1.50-1.69)	79.7	<0.0001		9	1.45 (1.27-1.65)	74.3	<0.0001	
Menopausal status											
Premenopausal		6	1.41 (1.37-1.45)	0	0.52	0.61/ 0.28[3]	0				0.58
Postmenopausal		15	1.54 (1.42-1.67)	89.6	<0.0001		5	1.41 (1.17-1.70)	85.2	<0.0001	
Pre- & postmenopausal		13	1.60 (1.48-1.72)	66.9	<0.0001		4	1.48 (1.31-1.67)	0	0.44	
Geographic location											
Europe		15	1.48 (1.37-1.60)	83.1	<0.0001	0.24	3	1.59 (1.22-2.09)	70.9	0.03	0.16
America		11	1.48 (1.37-1.60)	83.1	<0.0001		6	1.34 (1.22-1.48)	44.2	0.11	
Asia		2	1.47 (0.84-2.57)	63.8	0.10						
Number of cases											
Cases <249		13	1.59 (1.47-1.73)	47.3	0.03	0.17	4	1.42 (1.22-1.66)	0	0.43	0.84
Cases 250<500		7	1.59 (1.44-1.76)	80.0	<0.0001		2	1.37 (1.10-1.70)	64.1	0.10	
Cases ≥500		8	1.47 (1.37-1.58)	92.0	<0.0001		3	1.50 (1.14-1.96)	91.9	<0.0001	
Study quality											
0-3		0				0.15	0				0.59
4-6		4	1.74 (1.60-1.90)	0	0.80		2	1.33 (1.06-1.67)	0	0.98	
7-9		24	1.52 (1.45-1.60)	82.9	<0.0001		7	1.47 (1.27-1.71)	80.6	<0.0001	
Hormone replacement therapy use											
Never		6	1.65 (1.33-2.05)	97.7	<0.0001	0.005	0				NC
Ever		5	1.10 (1.06-1.14)	0	0.51		0				
Adjustment for confounders											
Parity	Yes	11	1.53 (1.42-1.64)	84.9	<0.0001	0.75	6	1.44 (1.24-1.68)	82.4	<0.0001	0.88
	No	17	1.55 (1.46-1.66)	76.7	<0.0001		3	1.46 (1.13-1.90)	26.6	0.26	
Age at menarche	Yes	7	1.47 (1.34-1.61)	82.3	<0.0001	0.19	6	1.49 (1.24-1.79)	83.8	<0.0001	0.61
	No	21	1.58 (1.50-1.66)	74.5	<0.0001		3	1.39 (1.22-1.58)	0	0.90	

Age at menopause	Yes	7	1.48 (1.36-1.60)	79.7	<0.0001	0.31	5	1.49 (1.24-1.78)	84.3	<0.0001	0.57
	No	21	1.57 (1.50-1.65)	73.7	<0.0001		4	1.33 (1.14-1.56)	24.5	0.26	
HRT use	Yes	8	1.45 (1.36-1.55)	72.0	0.0001	0.11	3	1.36 (1.18-1.56)	59.8	0.08	0.97
	No	20	1.59 (1.51-1.67)	74.6	<0.0001		5	1.33 (1.19-1.49)	7.2	0.37	
OC use	Yes	9	1.45 (1.35-1.55)	76.7	<0.0001	0.04	6	1.44 (1.24-1.68)	82.4	<0.0001	0.88
	No	19	1.61 (1.54-1.68)	61.6	<0.0001		3	1.46 (1.13-1.90)	26.6	0.26	
Alcohol	Yes	4	1.64 (1.55-1.73)	51.6	0.10	0.37	2	1.96 (1.70-2.28)	0	0.73	0.003
	No	24	1.53 (1.44-1.61)	81.0	<0.0001		7	1.30 (1.23-1.39)	0	0.44	
Smoking	Yes	17	1.54 (1.45-1.63)	80.9	<0.0001	0.93	6	1.53 (1.28-1.83)	82.0	<0.0001	0.26
	No	11	1.55 (1.41-1.70)	81.5	<0.0001		3	1.27 (1.12-1.43)	0	0.88	
Physical activity	Yes	11	1.52 (1.40-1.65)	88.2	<0.0001	0.52	6	1.46 (1.24-1.73)	83.3	<0.0001	0.86
	No	17	1.57 (1.50-1.65)	60.5	0.001		3	1.44 (1.23-1.69)	0	0.62	
Dietary fat	Yes	2	1.53 (1.41-1.66)	0	0.35	0.84	1	1.56 (1.24-1.95)	NC	NC	0.70
	No	26	1.54 (1.47-1.62)	82.1	<0.0001		8	1.43 (1.25-1.65)	76.8	<0.0001	
Fiber	Yes	3	1.45 (1.31-1.61)	62.3	0.07	0.36	1	1.56 (1.24-1.95)	NC	NC	0.70
	No	25	1.56 (1.48-1.64)	81.3	<0.0001		8	1.43 (1.25-1.65)	76.8	<0.0001	
Adjustment for potential intermediates[4]											
Diabetes	Yes	7	1.50 (1.38-1.64)	86.6	<0.0001	0.46	2	1.35 (1.08-1.70)	72.2	0.06	0.56
	No	21	1.56 (1.47-1.66)	78.9	<0.0001		7	1.48 (1.26-1.74)	72.4	0.001	
Hypertension	Yes	4	1.36 (1.24-1.49)	75.7	0.006	0.01	2	1.37 (1.10-1.70)	64.1	0.10	0.65
	No	24	1.59 (1.52-1.66)	71.7	<0.0001		7	1.48 (1.25-1.74)	78.2	<0.0001	

n denotes the number of risk estimates

[1] P for heterogeneity within each subgroup,

[2] P for heterogeneity between subgroups with meta-regression analysis

[3] P for heterogeneity between subgroups between premenopausal and postmenopausal women, excluding studies with mixed menopausal status

[4] These factors may be considered intermediate factors in the analyses of body fatness and endometrial cancer risk.

1

Table 2: Subgroup analyses of weight, weight gain and height and endometrial cancer

		Weight, per 5 kg					**Weight gain, per 5 kg**					**Height, per 10 cm**				
		n	RR (95% CI)	I^2 (%)	P_h^1	P_h^2	*n*	RR (95% CI)	I^2 (%)	P_h^1	P_h^2	*n*	RR (95% CI)	I^2 (%)	P_h^1	P_h^2
All studies		8	1.18 (1.14-1.23)	66.8	0.004		7	1.16 (1.12-1.20)	50.8	0.06		12	1.15 (1.09-1.22)	60.7	0.003	
Duration of follow-up																
<10 yrs follow-up		3	1.21 (1.09-1.35)	86.1	0.0001	0.77	2	1.17 (1.10-1.24)	61.5	0.11	0.79	4	1.15 (1.04-1.26)	31.5	0.22	0.86
≥10 yrs follow-up		5	1.19 (1.15-1.22)	0	0.53		5	1.15 (1.10-1.21)	56.8	0.06		8	1.16 (1.07-1.24)	69.0	0.002	
Assessment of weight/height																
Measured		3	1.13 (1.09-1.17)	22.6	0.28	0.008	1	1.13 (1.06-1.19)			0.59	6	1.18 (1.08-1.30)	71.9	0.003	0.45
Self-reported		5	1.22 (1.18-1.26)	0	0.60		6	1.16 (1.12-1.21)	55.6	0.05		6	1.12 (1.04-1.22)	50.7	0.07	
Menopausal status																
Premenopausal		2	1.06 (0.99-1.14)	0	0.52	0.30/ 0.08[3]	0				0.72/ NC[3]	2	1.08 (0.93-1.25)	10.8	0.29	0.90/ 0.32[3]
Postmenopausal		4	1.23 (1.14-1.33)	77.7	0.004		2	1.15 (1.04-1.26)	85.1	0.01		4	1.22 (1.09-1.38)	66.9	0.03	
Pre- & postmenopausal		3	1.18 (1.13-1.24)	34.4	0.22		5	1.17 (1.13-1.20)	22.0	0.27		6	1.11 (0.99-1.24)	73.5	0.002	
Geographic location																
Europe		6	1.17 (1.11-1.22)	58.0	0.04	0.25	2	1.13 (1.07-1.20)	0	0.84	0.58	7	1.14 (1.06-1.22)	56.1	0.03	0.94
America		2	1.23 (1.15-1.32)	42.4	0.19		5	1.17 (1.12-1.22)	64.4	0.02		4	1.16 (1.04-1.30)	76.7	0.005	
Asia		0					0					1	1.08 (0.77-1.49)			
Number of cases																
Cases <249		6	1.20 (1.15-1.26)	30.3	0.21	0.14	2	1.13 (1.05-1.22)	0	0.82	0.37	4	1.22 (0.99-1.50)	60.9	0.05	0.96
Cases 250<500		1	1.20 (1.16-1.26)				3	1.15 (1.07-1.23)	77.0	0.01		2	1.00 (0.85-1.18)	0	0.58	
Cases ≥500		1	1.11 (1.08-1.15)				2	1.18 (1.15-1.22)	0	0.37		6	1.16 (1.10-1.23)	70.9	0.004	
Study quality																
0-3		0				0.29	0				0.92	0				0.18
4-6		3	1.22 (1.16-1.28)	0	0.38		1	1.15 (0.99-1.33)				1	1.47 (1.10-1.96)			
7-9		5	1.17 (1.11-1.23)	73.7	0.004		6	1.16 (1.12-1.20)	59.0	0.03		11	1.14 (1.08-1.21)	59.9	0.005	
Hormone therapy use																
Never		1	1.18 (1.12-1.34)			NC	0				NC	0				NC
Ever		1	1.04 (0.97-1.12)				0					0				
Adjustment for confounders																
Parity	Yes	4	1.18 (1.10-1.26)	79.5	0.002	0.74	5	1.16 (1.12-1.21)	65.6	0.02	0.62	8	1.14 (1.05-1.24)	67.3	0.003	0.70
	No	4	1.19 (1.13-1.26)	43.4	0.15		2	1.13 (1.05-1.22)	0	0.82		4	1.16 (1.07-1.25)	41.0	0.17	
Age at menarche	Yes	3	1.18 (1.10-1.27)	86.3	0.001	0.85	5	1.16 (1.10-1.21)	66.7	0.02	0.90	8	1.16 (1.08-1.24)	59.4	0.02	0.88

	No	5	1.19 (1.13-1.25)	26.1	0.25		2	1.17 (1.12-1.21)	0	0.82		4	1.15 (1.00-1.33)	58.4	0.07	
Age at menopause	Yes	3	1.18 (1.10-1.27)	86.3	0.001	0.85	4	1.18 (1.14-1.22)	41.2	0.17	0.07	3	1.05 (0.92-1.21)	33.3	0.22	0.21
	No	5	1.19 (1.13-1.25)	26.1	0.25		3	1.11 (1.06-1.15)	0	0.70		9	1.17 (1.11-1.24)	63.8	0.005	
HRT use	Yes	2	1.15 (1.07-1.25)	89.4	0.002	0.37	3	1.19 (1.13-1.25)	57.7	0.09	0.21	6	1.14 (1.03-1.25)	68.7	0.007	0.68
	No	6	1.20 (1.15-1.26)	30.3	0.21		4	1.14 (1.09-1.18)	26.1	0.26		6	1.16 (1.08-1.25)	57.4	0.04	
OC use	Yes	4	1.18 (1.10-1.26)	79.5	0.002	0.74	5	1.16 (1.12-1.21)	65.6	0.02	0.62	6	1.16 (1.01-1.34)	67.5	0.009	0.83
	No	4	1.19 (1.13-1.26)	43.4	0.15		2	1.13 (1.05-1.22)	0	0.82		6	1.14 (1.08-1.20)	55.0	0.05	
Alcohol	Yes	0				NC	0				NC	3	1.16 (1.10-1.22)	7.9	0.34	0.89
	No	8	1.18 (1.14-1.23)	66.8	0.004		7	1.16 (1.12-1.20)	50.8	0.06		9	1.15 (1.06-1.25)	68.2	0.001	
Smoking	Yes	4	1.18 (1.10-1.26)	79.5	0.002	0.74	4	1.18 (1.14-1.22)	41.2	0.17	0.07	10	1.15 (1.07-1.23)	58.8	0.009	0.70
	No	4	1.19 (1.13-1.26)	43.4	0.15		3	1.11 (1.06-1.15)	0	0.70		2	1.23 (0.95-1.60)	69.1	0.004	
Physical activity	Yes	2	1.17 (1.04-1.32)	88.4	0.003	0.60	5	1.15 (1.11-1.19)	49.6	0.09	0.22	6	1.11 (1.04-1.20)	43.1	0.12	0.27
	No	6	1.19 (1.15-1.23)	13.5	0.33		2	1.22 (1.15-1.30)	0	0.34		6	1.20 (1.09-1.32)	73.9	0.002	
Dietary fat	Yes	1	1.20 (1.16-1.26)			0.74	1	1.24 (1.16-1.33)			0.15	1	0.97 (0.80-1.17)			0.20
	No	7	1.18 (1.12-1.24)	64.9	0.009		6	1.15 (1.11-1.18)	37.0	0.16		11	1.16 (1.10-1.23)	60.3	0.005	
Fiber	Yes	2	1.15 (1.07-1.25)	89.4	0.002	0.37	2	1.18 (1.08-1.30)	76.5	0.04	0.56	2	1.00 (0.89-1.13)	0	0.69	0.08
	No	6	1.20 (1.15-1.26)	30.3	0.21		5	1.15 (1.11-1.20)	46.5	0.11		10	1.18 (1.11-1.24)	60.6	0.007	
Adjustment for potential intermediates[4]																
Diabetes	Yes	3	1.15 (1.08-1.24)	78.9	0.009	0.31	3	1.19 (1.13-1.25)	57.7	0.09	0.21	4	1.02 (0.92-1.14)	18.5	0.30	0.05
	No	5	1.21 (1.15-1.27)	42.2	0.14		4	1.14 (1.09-1.18)	26.1	0.26		8	1.19 (1.12-1.26)	62.4	0.009	
Hypertension	Yes	2	1.15 (1.07-1.25)	89.4	0.002	0.37	3	1.15 (1.07-1.23)	77.0	0.01	0.64	2	1.00 (0.89-1.13)	0	0.69	0.08
	No	6	1.20 (1.15-1.26)	30.3	0.21		4	1.17 (1.14-1.21F)	0	0.56		10	1.18 (1.11-1.24)	60.6	0.007	

n denotes the number of risk estimates

[1] P for heterogeneity within each subgroup,

[2] P for heterogeneity between subgroups with meta-regression analysis

[3] P for heterogeneity between subgroups between premenopausal and postmenopausal women, excluding studies with mixed menopausal status

[4] These factors may be considered intermediate factors in the analyses of body fatness and endometrial cancer risk.

Figure 1. BMI and endometrial cancer incidence

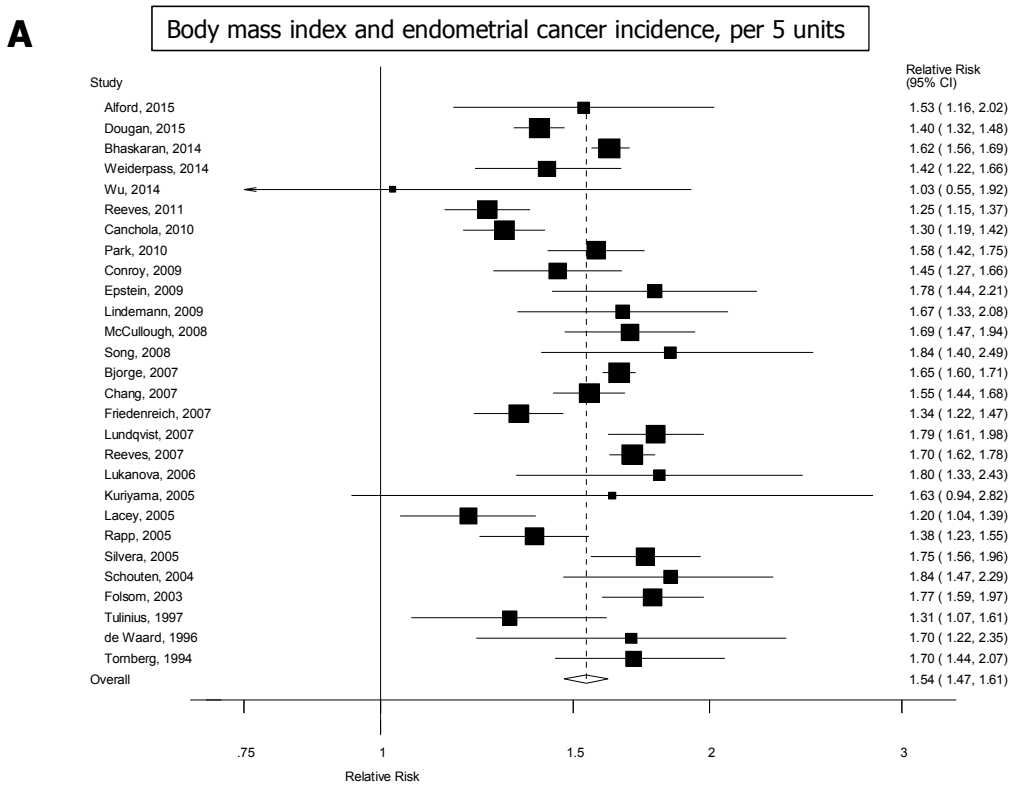

Figure 2. BMI and endometrial cancer mortality, and BMI in young adulthood and endometrial cancer

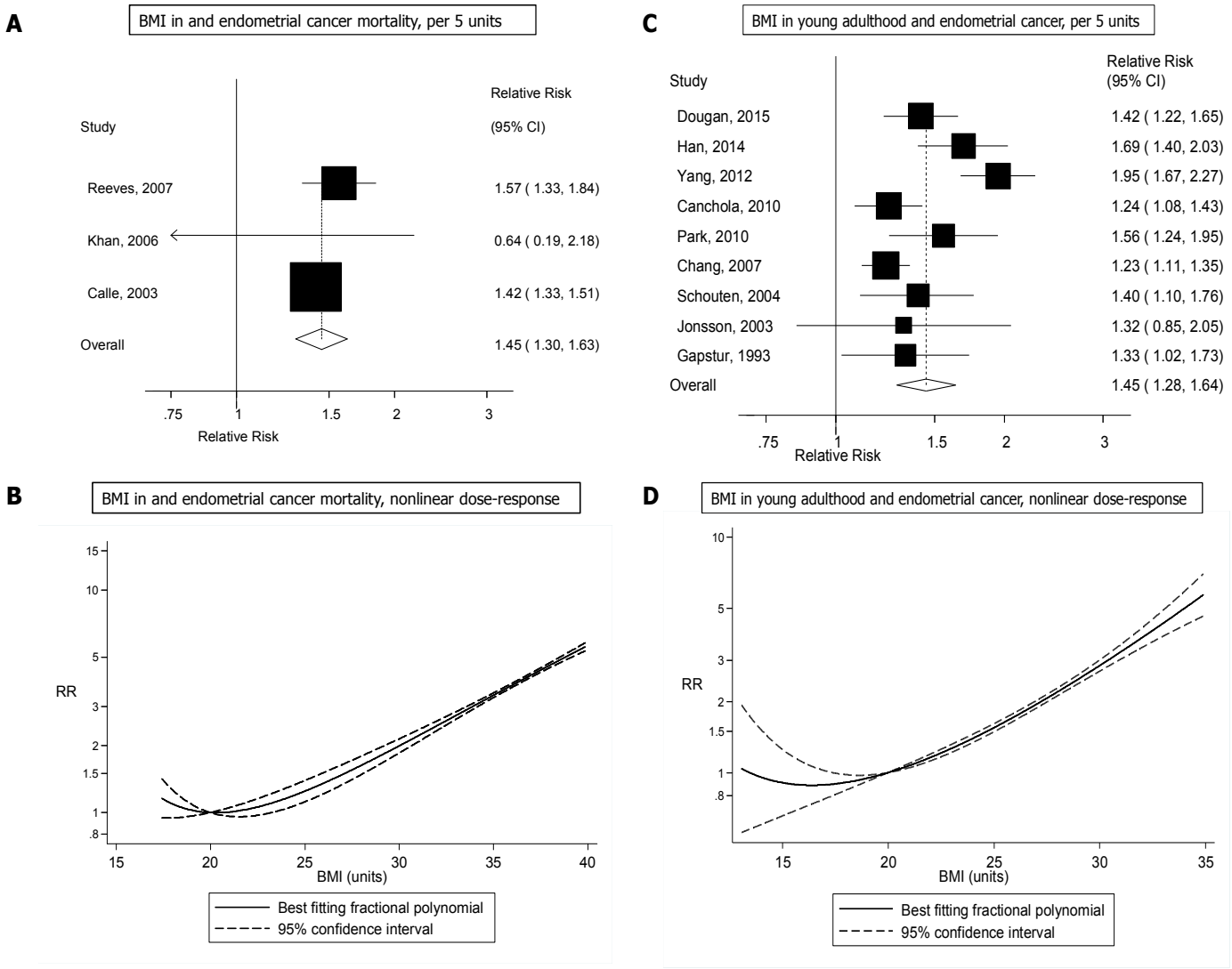

Figure 3. Weight and weight changes and endometrial cancer

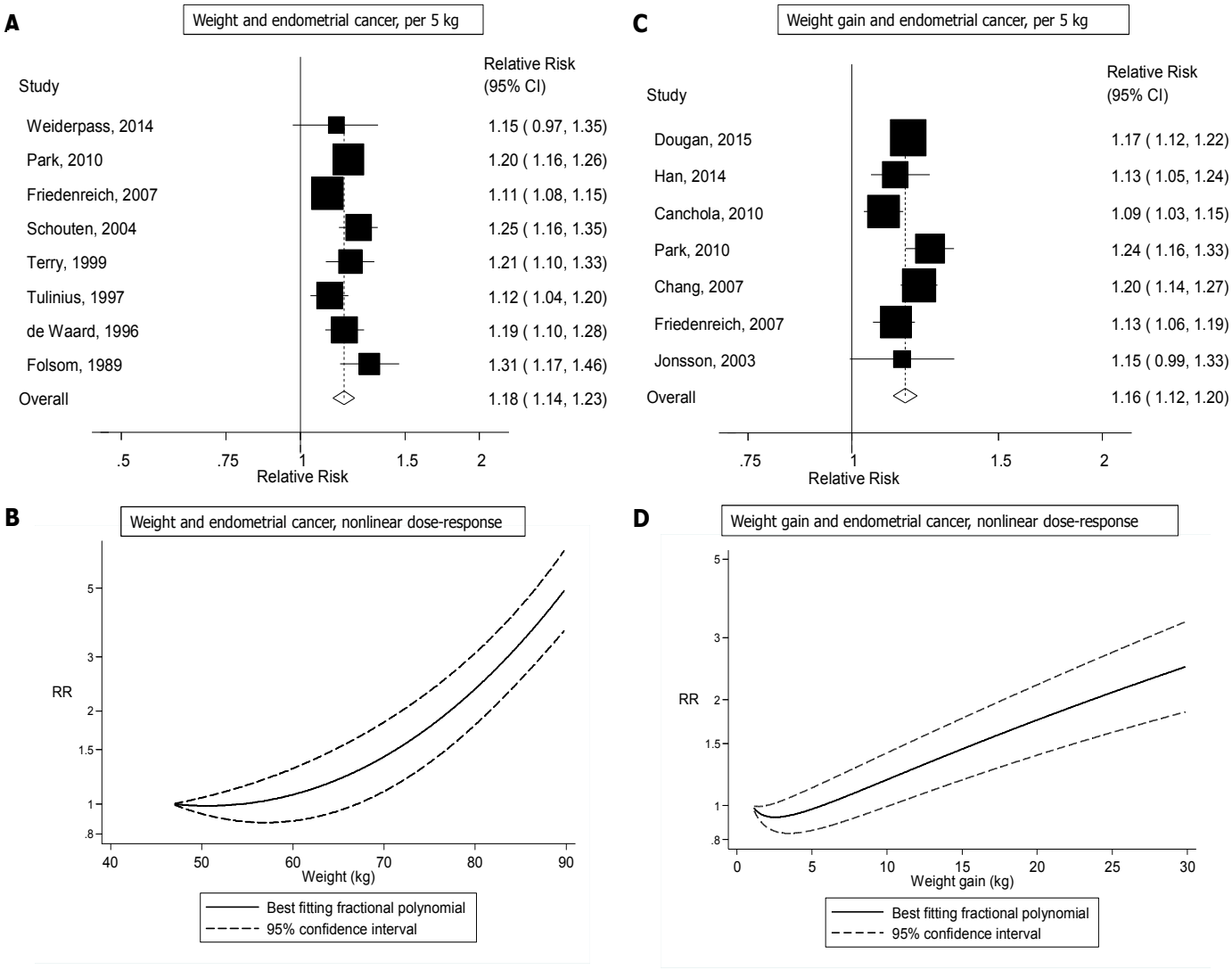

Figure 4. Waist circumference and waist-to-hip ratio and endometrial cancer

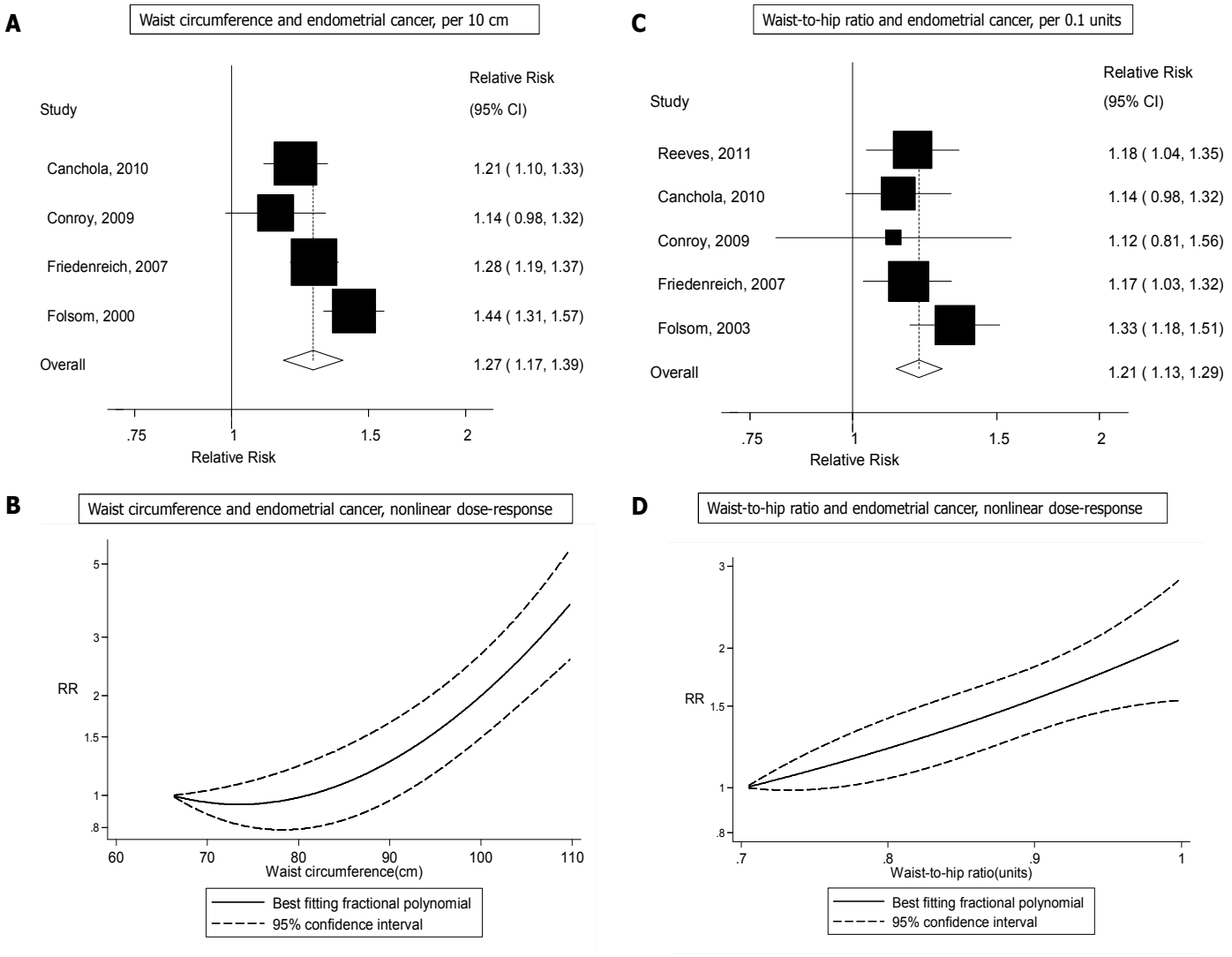

Figure 5: Hips circumference and endometrial cancer