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Abstract
Objective To examine the association between anthropometry and endometrial cancer, particularly by menopausal status and exogenous hormone use subgroups.
Methods Among 223,008 women in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, there were 567 incident endometrial cancer cases during 6.4 years of follow-up. The analysis was performed with Cox proportional hazards modeling.
Results Weight, body mass index (BMI), waist and hip circumferences and waist–hip ratio (WHR) were strongly associated with increased risk of endometrial cancer. The relative risk (RR) for obese (BMI 30–

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< 40 kg/m^2) compared to normal weight (BMI < 25) women was 1.78, 95% CI = 1.41–2.26, and for morbidly obese women (BMI ≥ 40) was 3.02, 95% CI = 1.66–5.52. The RR for women with a waist circumference of ≥88 cm vs. <80 cm was 1.76, 95% CI = 1.42–2.19. Adult weight gain of ≥20 kg compared with stable weight (±3 kg) increased risk independent of body weight at age 20 (RR = 1.75, 95% CI = 1.11–2.77). These associations were generally stronger for postmenopausal than premenopausal women, and oral contraceptives never-users than ever-users, and much stronger among never-users of hormone replacement therapy compared to ever-users.

Conclusion Obesity, abdominal adiposity, and adult weight gain were strongly associated with endometrial cancer risk. These associations were particularly evident among never-users of hormone replacement therapy.

Keywords Anthropometry · Endometrial cancer · Etiology · Risk factors · Obesity · Adiposity · Mechanisms · Hormone replacement therapy

Introduction

The International Agency for Research on Cancer (IARC) classified the evidence on the association of obesity and endometrial cancer risk as 'convincing' in 2002 [1] stating that the relative risk of obese (body mass index (BMI) ≥ 30 kg/m^2) compared to normal weight (BMI < 25) women is two- to three-fold. It was unclear at that time whether there was a linear increase in risk with increasing BMI or if the risk existed for the highest category of BMI only. It was hypothesized that the inconsistency between studies in the shape of the relation between BMI and endometrial cancer risk might be attributable to misclassification from the use of weight or BMI as a measure of obesity, because they are imperfect measures of adiposity [1]. Alternatively, the inconsistencies in study results could be due to differences in the underlying biologic mechanisms in premenopausal versus postmenopausal women [2], or due to body fat distributions that may vary between populations or by ethnicity [1].

Few studies have examined the association between body measures and endometrial cancer risk by

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menopausal status or by age group and the numbers of premenopausal women have been small in previous studies [1]. Adult weight gain per se has been found to be linearly associated with endometrial cancer risk in some studies but the results are inconsistent [3–13]. Adiposity and fat distribution has been assessed in previous studies using BMI, waist–hip ratio (WHR), waist-to-thigh ratio, subscapular skinfold and subscapular-to-thigh skinfold ratio [4, 5, 14–19]. It is unclear which of these measures is the most etiologically relevant to endometrial cancer development, as results from previous studies have also been inconsistent [1]. The use of exogenous hormones such as oral contraceptives (OC) and hormone replacement therapy (HRT) influence circulating estrogen and progesterone levels and may modify the effect of obesity on endometrial cancer risk [20], yet few studies [8, 21] have examined interactions between general and central adiposity and exogenous hormones. We conducted an analysis in the European Prospective Investigation into Cancer and Nutrition (EPIC), a heterogeneous and large cohort, to examine the association between anthropometric factors and endometrial cancer risk, particularly by menopausal status and exogenous hormone use subgroups.

Methods

Study cohort

EPIC is an ongoing multi-center, prospective cohort study, designed primarily to investigate the associations between dietary and lifestyle factors and cancer risk. The design, study population, and baseline data collection methods have been previously described in detail [22, 23]. In brief, standardized questionnaire data on dietary and lifestyle factors were collected from approximately 370,000 women and 150,000 men, enrolled between 1992 and 2000 in 23 centers throughout 10 western European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, The Netherlands, and United Kingdom) [23]. Participants were mainly between 35 and 70 years of age at enrollment, and were recruited from the general population residing within defined geographic areas (i.e., town or province), with some exceptions: women who were members of a health insurance scheme for state school employees (France); women attending breast cancer screening (Utrecht, The Netherlands); blood donors (some centers in Italy and Spain) and a cohort with about half the participants who were vegetarians (Oxford 'health conscious' cohort). Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all local recruiting institutions. All participants provided written informed consent.

For the present analysis, we excluded a priori the following women: 19,953 with prevalent cancer at enrollment, 1,293 with missing follow-up data, 35,444 with a hysterectomy at baseline, 6,091 women who were in the top or bottom 1% of the distribution of the ratio of energy intake to estimated energy requirement [24], and 3,586 members with no dietary or lifestyle data. We further restricted the analysis to women who had their baseline anthropometric measurements taken by trained observers at study centers (n = 191,623) or women with self-reported measurements that could be corrected for reporting error using age- and sex-specific linear regression model prediction equations (Oxford 'health conscious' cohort, n = 31,385) [25, 26]. Thus, 78,635 women with missing height and weight measurements were excluded, comprising all study subjects from Norway, about 71% of French participants, 3% of participants in the UK Oxford 'health conscious' cohort, and less than 1% in other centers. A total of 223,008 women were included in this analysis. Of these women, waist and hip circumference measurements were missing for 14,610 (6.6%) and 14,988 (6.7%) women, respectively, including all 12,187 women from Umeå, Sweden.

Measurement of anthropometric characteristics and other predictor variables

Details on the standardized procedures for taking anthropometric measurements in the EPIC study centers have been previously described in detail [25]. Briefly, weight was measured to the nearest 0.1 kg and height was measured to the nearest 0.1, 0.5, or 1.0 cm depending on the study center, in subjects wearing no shoes. Waist circumference was measured either at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest. Hip circumference was measured at the widest circumference or over the buttocks. Weight, waist, and hip measurements were corrected to account for protocol differences between

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centers in clothing worn by participants during body measurements [25]. Adult weight change was estimated as the difference between measured weight at study enrollment and recalled weight at age 20 (25 years in one center). However, data on recalled weight were not available for all centers [27], thus the weight change analyses were limited to a sub-cohort of 264 cases and 106,272 non-cases.

The baseline assessment of physical activity, including occupational, household and recreational activities, has been previously described in detail [28]. A summary index of total physical activity (inactive, moderately inactive, moderately active, active) was calculated by cross-tabulating the level of occupational activity (non-worker, sedentary, standing, manual, heavy manual, and unknown) with quartiles of combined recreational and household activities calculated in MET-hours/week [29, 30]. Diet over the previous 12 months was assessed at the time of enrollment using country-specific, validated dietary assessment instruments [23, 31]. Data on lifestyle, health, and socio-demographic characteristics were collected via standardized questionnaires that included menstrual and reproductive history, use of OCs and postmenopausal HRT, medical history, lifetime history of tobacco smoking and alcohol consumption, brief occupational history and level of education. Women who were currently using HRT or OCs at baseline or who had previously used HRT or OCs prior to study entry were classified as 'ever-users' of HRT or OCs, respectively. Women who, at study entry, had never used and were not currently using HRT or OCs were classified as 'never-users' of HRT or OCs, respectively. Menopausal status at enrollment was defined as follows: women were 'premenopausal' if they reported having had regular menses over the past 12 months; 'postmenopausal' if they reported not having had any menses over the past 12 months, or if they had a bilateral ovariectomy; and 'perimenopausal/unknown' if they reported irregular menses over the past 12 months (1–9 cycles) or if they indicated having had menses over the past 12 months but were no longer menstruating at the time of recruitment. Women with incomplete or missing questionnaire data, or who reported current use of exogenous hormones, were classified as premenopausal if they were less than 46 years of age, perimenopausal/unknown if they were between 46 and 55 years of age, and postmenopausal if they were older than 55 years. All women were included in all of the analyses, except for the subgroup analysis by menopausal status that excluded perimenopausal/unknown women, and the subgroup analysis by ever HRT use that was among postmenopausal women only.

Follow-up for cancer incidence and vital status

Incident cases were identified through population-based cancer registries, except in France, Germany, and Greece, where a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin was used. Data on vital status in most EPIC study centers were collected from mortality registries at the regional or national level, in combination with data collected by active follow-up (Greece). Vital status was known for 98.4% of all EPIC participants as of April 2004. Women were followed from the date of enrollment until endometrial cancer diagnosis, death, emigration, or end of the follow-up period. The closure date for this study period for each EPIC center was the date of the last complete follow-up for both cancer incidence and vital status, which varied between December 1999 and March 2004 between EPIC centers. A total of 567 incident cases of endometrial cancer were diagnosed during the follow-up period. The cancer diagnosis was confirmed by histology for 86% of cases, by clinical examination for 11%, and the remaining 3% by self-report, tomography scan, surgery, autopsy, or by death certificate. Detailed morphology was specified for 223 (39%) cases, of which 203 (91%) were endometrioid, 8 (4%) serous, 5 (2%) mucinous, 5 (2%) clear cell, and 2 (1%) undifferentiated [32].

Statistical analyses

Descriptive statistics were calculated as age- and center-adjusted means for continuous variables, or as percentages for categorical variables. All analyses were performed using SAS Statistical Software, version 9.1 (SAS Institute, Cary, NC, USA), and all statistical tests were two-sided. We analyzed the association between anthropometric variables and risk of endometrial cancer by calculating incidence rate ratios as estimates of relative risks (RR) using Cox proportional hazard models. Age was used as the underlying time variable, with entry and exit time defined as the subject's age at recruitment and age at endometrial cancer diagnosis or censoring (death, lost to follow-up, end of follow-up), respectively. Models were stratified by study center to account for center effects such as follow-up procedures and questionnaire design, and by age at recruitment (in one-year categories), to be less sensitive to violations of the proportional hazards assumption.

Weight, height, hip, and WHR were categorized into quartiles, and BMI and waist were categorized into pre-defined, internationally standardized categories:

BMI < 25 [normal weight], ≥25 to < 30 [overweight], ≥30 to <40 kg/m^2 [obese], ≥40 kg/m^2 [morbid obese]; waist circumference <80, 80 to <88, ≥88 cm [1]. Cut-points were based on the overall cohort distribution for all centers combined. Trend tests were estimated on integer scores applied to the anthropometric categories or quartiles, and entered as a continuous term in the regression models. In addition, we examined the anthropometric measures as continuous variables in the models, to estimate the relative risk per unit change in the variable.

Two sets of models are presented: the 'crude' model stratified by age and center; and the fully adjusted multivariate model stratified by age and center and adjusted for potential confounders: total physical activity level (inactive, moderately inactive, moderately active and active, missing), age at menarche (<12, 12, 13, 14, ≥15, missing), menopausal status (premenopausal, perimenopausal, postmenopausal), age at menopause (<43, 43–46, 47–49, 50–51, 52–53, ≥54, missing), number of full-term pregnancies (0, 1, 2, 3, ≥4, missing), age at birth of last child (<27, 27–29, 30–32, ≥33, missing), use of OCs (ever, never, missing), use of HRT (ever, never, missing), education (none, primary school completed, technical/professional school, secondary school, university degree, missing), cigarette smoking status (never, former, current, unknown), hypertension (yes, no, unknown), diabetes (yes, no, unknown), fruit and vegetable intake (grams/day in quartiles), fiber intake (grams/day in quartiles), carbohydrate intake (grams/day in quartiles), energy intake (grams/day in quartiles). All potential confounders were retained in the multivariate models, as the exclusion of single or multiple factors did not result in more precise estimates for the effects of anthropometric measures, thus, there was no advantage in using more parsimonious models [33]. In addition, we examined the effect of mutual adjustment of body measures to determine whether fat distribution or general obesity were determinants of risk.

We examined whether or not the association between anthropometric factors and endometrial cancer risk differed according to specific subgroups, by adding subgroup interaction terms to the multivariate models. The following subgroups were examined: menopausal status, use of OCs, use of HRT, total physical activity level, quartiles of energy intake, and age groups by decade year and country. Heterogeneity of BMI (continuous variable) by country was explored by meta-regression using the Genmod procedure. The data satisfied the proportional hazards assumption that was checked by adding interaction terms for BMI and waist circumference (separately) with follow-up time (years) to the models.

Results

There were 567 endometrial cancer cases diagnosed in this cohort of 223,008 women from EPIC during an average 6.4 (SD 1.7) years of follow-up (Table 1). The women were 50.2 (SD 10.9) years on average and 30.6% of the cohort were classified as overweight (BMI >25–<30) and 14.5% were obese (BMI ≥30). The prevalence of overweight ranged from 18.7% in the health conscious cohort in the United Kingdom to 41.8% in Spain. Obesity prevalence ranged from 5.4% in the French women to 35.5% in Greece. Women who developed endometrial cancer during follow-up were fairly comparable to those who did not develop endometrial cancer in this cohort with the exception of anthropometric measurements, age, use of exogenous hormones, education, and self-reported hypertension (Table 2).

Body weight and BMI were statistically significantly associated with risk of endometrial cancer (Table 3). Women in the highest quartile of weight versus those in the lowest quartile (>72.4 kg vs. <58 kg) had a relative risk of 1.74, 95% CI = 1.35–2.23, $p_{trend} < 0.0001$. Overweight participants (BMI ≥ 25 – <30) did not have a statistically significant increased risk. The multivariate risk for obese women was 1.78, 95% CI = 1.41–2.26 and for morbidly obese women the risk was 3.02, 95% CI = 1.66–5.52 ($p_{trend} = < 0.0001$). The associations for weight and BMI were slightly attenuated after additional adjustment for WHR. No association between height and endometrial cancer risk was found. After adjustment for BMI, associations between measures of fat distribution (waist and hip circumferences and WHR) and endometrial cancer risk were confined to a statistically significant increased risk with higher waist circumference (Table 3). Women with a waist circumference of ≥88 cm compared to those in the referent category (<80 cm) had a relative risk of 1.50, 95% CI = 1.10–2.04 after adjustment for BMI. A statistically significant association between hip circumference quartiles and endometrial cancer risk was noted only in the multivariate model without adjustment for BMI for which the risk for the highest compared to the lowest quartile was 1.51, 95% CI = 1.17–1.94, ($p_{trend} = 0.0002$). A similar pattern of associations was noted for WHR.

Within a sub-cohort of 264 cases and 106,272 non-cases for whom data on recalled weight at age 20 had been collected, an elevated risk of 1.75, 95% CI = 1.11–2.77 was found among women who had gained ≥20 kg or more between age 20 and time of enrollment compared to women who stayed within ±3 kg of their weight at age 20 for both multivariate models with and without

Table 1 Size of the EPIC cohort for the analyses of anthropometry and endometrial cancer, by country

Country	Cohort size	Age at recruitment (mean, SD)	Number of years of follow-up (mean, SD)	Person-years	Number of endometrial cancer cases	% Overweight BMI 25–<30 kg/m^2	% Obese BMI ≥30 kg/m^2
France	17,725	52.5 (6.4)	8.5 (0.8)	150,443	65	20.0	5.4
Italy	27,576	50.3 (8.1)	6.2 (1.5)	170,351	73	34.7	14.2
Spain	22,568	47.9 (8.4)	6.6 (1.0)	148,832	56	41.8	29.8
United Kingdom							
– health conscious	31,385	42.0 (13.8)	5.3 (1.2)	167,734	22	18.7	5.6
– general population	13,167	56.6 (9.4)	5.6 (1.4)	74,292	49	33.5	14.2
The Netherlands	22,670	49.7 (12.0)	6.5 (1.9)	146,954	54	31.4	10.9
Greece	13,687	52.8 (12.6)	3.7 (0.7)	50,953	11	37.0	35.5
Germany	23,546	48.1 (9.0)	5.9 (1.4)	137,821	33	29.8	14.7
Sweden	26,197	52.0 (10.7)	7.8 (1.6)	203,870	90	30.0	11.1
Denmark	24,487	56.7 (4.4)	6.7 (1.0)	165,213	114	33.7	13.5
Total	**223,008**	**50.2 (10.9)**	**6.4 (1.7)**	**1,416,463**	**567**	**30.6**	**14.5**

adjustment for weight at age 20 (Table 3). When stratified by menopausal status at baseline, the association between adult weight gain and cancer risk was stronger among postmenopausal women than premenopausal women (data not shown). Weight loss was not associated with endometrial cancer risk in this cohort, although this analysis was limited by a small number of cases since only a few women had lost weight.

The interactions between these anthropometric factors and endometrial cancer risk by menopausal status at baseline were not statistically significant ($p_{\text{interaction}}$ all ≥0.10). However, we observed stronger associations and trends for postmenopausal than premenopausal women for weight, BMI, and hip circumference while for waist circumference and WHR, we found somewhat greater risks among premenopausal than postmenopausal women (Table 4).

Evidence for effect modification of the association between anthropometry and endometrial cancer risk by HRT use at baseline was observed (Table 5) ($p_{\text{interaction}}$ for weight, BMI, waist and hip circumference all <0.05, and for waist–hip ratio = 0.08). Women who never used HRT had an approximate doubling in risk in the highest quantile of weight, BMI, waist and hip circumferences and WHR compared to the referent categories. No statistically significant associations were observed among ever HRT users for any of the body measures tested. We also considered effect modification of this association by current HRT use (data not shown) and found similar or stronger associations among women not currently using HRT as observed with never-users. We also examined the risk of endometrial cancer associated with each combined BMI–HRT category against the reference category of normal weight, never HRT users (data not shown). Compared to the referent group, overweight never HRT users had no increased risk, but normal weight and overweight ever HRT users had a 70% higher risk, reflecting the increased exposure to estrogens in many HRT formulations. However, this higher underlying risk among ever HRT users than never HRT users was not observed among obese women (BMI ≥ 30), for whom both never-users and ever-users had a 2.3-fold increased risk compared to the referent group. Thus, obesity increased risk to a greater extent among never-users than ever-users.

The possibility of effect modification by ever use of OCs reported at baseline was also examined (Table 6). The associations were generally stronger in never OC users compared to ever OC users, although the tests for interaction were not statistically significant ($p_{\text{interaction}}$ all ≥ 0.05). The tests for linear trend were highly statistically significant among never OC users but only marginally statistically significant among ever OC users. There were no statistically significant interactions for the other possible effect modifiers considered in this analysis including physical activity, energy intake, length of follow-up, or age. The relative risk estimates were generally slightly stronger when we restricted the analysis to known Type I tumors (generally estrogen-dependent endometrioid adenocarcinomas; data not shown) [32].

We found statistically significant heterogeneity by country for BMI ($p_{\text{heterogeneity}}$ = 0.03), but not for waist

Table 2 Demographic and lifestyle characteristics of the incident endometrial cancer cases and women who did not develop endometrial cancer in the EPIC cohort, n = 223,008

Characteristic	Endometrial cancer incident cases (n = 567)	Women without endometrial cancer (n = 222,441)
Age at recruitment (years) (mean, SD)	54.4 (9.4)	50.5 (11.4)
Education (%)		
None	4.5	5.5
Primary school completed	30.1	24.1
Technical/professional school	25.7	24.5
Secondary school	22.7	22.2
University degree	17.1	23.8
Menopausal status (%)		
Premenopausal	16.1	40.3
Perimenopausal	17.6	14.3
Postmenopausal	66.3	45.5
Reproductive and hormone factors (mean, SD)		
Age at menarche (years)	12.8 (1.5)	13.0 (1.9)
Age at menopause (years)	51.0 (4.3)	49.5 (5.9)
Age at first full-term pregnancy[a] (years)	25.0 (4.3)	25.1 (5.1)
Number of full-term pregnancies[a]	2.2 (1.0)	2.4 (1.2)
Age at birth of last child[a] (years)	29.3 (4.8)	29.9 (5.7)
Hormone replacement therapy (ever used; %)[b]	44.8	36.9
Oral contraceptives (ever used; %)	40.6	58.5
Nulliparous	17.6	18.7
Dietary intake (mean, SD)		
Energy intake (kcal/day)	1,999.2 (512.7)	2,020.8 (625.9)
Fruits and vegetables (g/day)	520.3 (243.1)	504.2 (296.8)
Fiber (g/day)	22.8 (7.1)	22.4 (8.6)
Carbohydrate (g/day)	232.8 (68.4)	232.5 (83.5)
Smoking status (%)		
Never smoker	61.9	57.0
Ex-smoker	21.2	22.7
Current smoker	16.9	20.3
Hypertension (%)	30.3	20.4
Diabetes (%)	3.5	2.3
Anthropometric factors (mean, SD)		
Body Mass Index (kg/m^2)	26.8 (4.2)	25.5 (5.1)
% Obese (BMI ≥30 kg/m^2)	24.2	14.4
Weight at study entry (kg)	69.1 (11.4)	65.8 (14.0)
Weight[c] at age 20 (kg)	56.9 (8.0)	56.6 (9.6)
Weight[c] change since age 20 (kg)	12.6 (9.9)	10.0 (11.8)
Waist–hip ratio	0.802 (0.1)	0.796 (0.1)
Waist circumference (cm)	83.5 (10.1)	80.8 (12.3)
Hip circumference (cm)	103.9 (8.6)	101.3 (10.5)
Height (cm)	160.8 (5.9)	160.7 (7.2)
Total physical activity (%)		
Inactive	17.4	18.2
Moderately inactive	36.9	33.9
Moderately active	39.4	40.0
Active	6.4	7.9

SD = standard deviation

Missing values were excluded from percentage calculations. Continuous variables are presented as means and standard deviations and are adjusted by age and center, except age that is adjusted by center only

[a] Among parous women

[b] Among postmenopausal women only (337 cases and 92,310 non-cases)

[c] Limited to a sub-cohort of 264 cases and 106,272 non-cases with complete data on recalled weight at age 20

circumference or WHR ($p_{\text{heterogeneity}}$ = 0.09 and 0.50, respectively). The multivariate hazards ratios per 1-unit increase in BMI ranged from 1.02, 95% CI = 0.97–1.07 (Sweden) to 1.13, 95% CI = 1.07–1.19 (The Netherlands) with the pooled estimate for all EPIC centers at 1.06, 95% CI = 1.04–1.08. In the meta-regression analyses used to explore possible sources of the heterogeneity of the association of BMI with endometrial cancer risk, the following variables did not independently explain the heterogeneity: geographic

Table 3 Hazard ratio estimates of endometrial cancer by anthropometric factors

Anthropometric factor	Number of cases[a]	Number of person-years	Hazard ratio and 95% confidence interval		
			Adjustment factors		
			Age and center	Multivariate[b]	Multivariate[b] and other body measure[c]
Weight (kg) in quartiles					
≤58.0	103	353,899	1.00	1.00	1.00
>58.0–<64.5	120	359,657	1.08 (0.82–1.40)	1.08 (0.82–1.41)	1.00 (0.75–1.31)
≥64.5–72.4	128	354,619	1.06 (0.81–1.38)	1.06 (0.81–1.38)	0.95 (0.72–1.27)
>72.4	216	348,288	1.76 (1.38–2.24)	1.74 (1.35–2.23)	1.61 (1.23–2.12)
p_{trend}			<0.0001	<0.0001	0.0003
HR per 5 kg			1.11 (1.08–1.15)	1.11 (1.08–1.15)	1.11 (1.07–1.15)
Height (cm) in quartiles					
≤157.0	150	345,636	1.00	1.00	1.00
>157.0–162.0	147	343,113	1.07 (0.85–1.36)	1.09 (0.86–1.38)	1.02 (0.81–1.30)
>162.0–166.5	147	375,224	1.02 (0.80–1.31)	1.03 (0.81–1.32)	0.92 (0.72–1.18)
>166.5	123	352,489	1.06 (0.81–1.38)	1.09 (0.83–1.42)	0.90 (0.68–1.19)
p_{trend}			0.77	0.64	0.34
HR per 5 cm			1.01 (0.94–1.08)	1.01 (0.94–1.09)	0.95 (0.89–1.03)
Body mass index (BMI; kg/m^2)					
<25	247	789,410	1.00	1.00	1.00
≥25–<30	183	431,811	1.11 (0.91–1.35)	1.11 (0.91–1.36)	1.05 (0.85–1.31)
≥30–<40	125	183,777	1.80 (1.43–2.25)	1.78 (1.41–2.26)	1.72 (1.32–2.23)
≥40	12	11,465	3.06 (1.70–5.52)	3.02 (1.66–5.52)	2.97 (1.61–5.48)
p_{trend}			<0.0001	<0.0001	<0.0001
HR per 1 kg/m^2			1.06 (1.04–1.08)	1.06 (1.04–1.08)	1.06 (1.04–1.08)
Waist circumference[a] (cm)					
<80	224	734,164	1.00	1.00	1.00
80–<88	115	285,531	1.06 (0.85–1.34)	1.08 (0.86–1.36)	1.08 (0.83–1.40)
≥88	191	286,150	1.73 (1.40–2.13)	1.76 (1.42–2.19)	1.50 (1.10–2.04)
p_{trend}			<0.0001	<0.0001	0.02
HR per 5 cm			1.12 (1.08–1.17)	1.13 (1.09–1.17)	1.10 (1.04–1.17)
Hip circumference[a] (cm) in quartiles					
≤94.5	109	329,105	1.00	1.00	1.00
>94.5–<100.0	98	322,116	0.83 (0.63–1.09)	0.82 (0.62–1.08)	0.82 (0.62–1.08)
≥100.0–<106.0	117	327,268	0.89 (0.68–1.16)	0.87 (0.67–1.14)	0.87 (0.64–1.18)
≥106.0	207	326,051	1.54 (1.21–1.96)	1.51 (1.17–1.94)	1.27 (0.89–1.83)
p_{trend}			<0.0001	0.0002	0.28
HR per 5 cm			1.16 (1.11–1.21)	1.15 (1.10–1.21)	1.13 (1.05–1.21)
Waist–hip ratio[a] (WHR) in quartiles					
≤0.742	78	321,535	1.00	1.00	1.00
>0.742–<0.785	131	330,561	1.32 (0.99–1.75)	1.34 (1.01–1.78)	1.32 (0.99–1.75)
≥0.785–0.831	147	331,564	1.35 (1.02–1.79)	1.39 (1.05–1.85)	1.31 (0.98–1.75)
>0.831	174	320,183	1.52 (1.15–2.01)	1.58 (1.19–2.10)	1.33 (0.98–1.80)
p_{trend}			0.007	0.003	0.13
HR per 0.1 unit			1.15 (1.02–1.30)	1.17 (1.03–1.32)	1.06 (0.92–1.22)
Weight change (kg) since age 20, in subcohort[d]					
<–3	12	47,058	0.92 (0.47–1.82)	1.00 (0.51–1.98)	1.01 (0.51–1.99)
–3 to <3 (*reference*)	28	120,745	1.00	1.00	1.00
3–<10	70	198,448	1.13 (0.73–1.76)	1.12 (0.72–1.74)	1.12 (0.72–1.75)
10–<15	46	109,618	1.08 (0.68–1.74)	1.07 (0.67–1.72)	1.07 (0.67–1.73)
15–<20	42	71,449	1.41 (0.87–2.29)	1.39 (0.86–2.26)	1.40 (0.86–2.27)

Table 3 Hazard ratio estimates of endometrial cancer by anthropometric factors

Anthropometric factor	Number of cases[a]	Number of person-years	Hazard ratio and 95% confidence interval		
			Adjustment factors		
			Age and center	Multivariate[b]	Multivariate[b] and other body measure[c]
≥20	66	89,368	1.71 (1.10–2.68)	1.75 (1.11–2.77)	1.75 (1.11–2.77)
p_{trend}			0.003	0.004	0.004
HR per 5 kg			1.12 (1.06–1.18)	1.13 (1.06–1.19)	1.13 (1.06–1.19)

[a] Some data are unknown for waist circumference (37 cases and 14,573 non-cases), hip circumference (36 cases and 14,819 non-cases), and WHR (37 cases and 14,951 non-cases). The totals and tests for trend for these variables exclude the unknown values

[b] Stratified by age and center, and adjusted for total physical activity level, age at menarche, menopausal status, age at menopause, number of full-term pregnancies, age at birth of last child, ever use of oral contraceptives, ever use of hormone replacement therapy, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fiber intake, carbohydrate intake, and energy intake

[c] The models for BMI and weight were additionally adjusted for WHR (quartiles); the models for waist, hip and WHR were adjusted for BMI (four WHO categories); the model for height was adjusted for weight (quartiles); the model for weight change was adjusted for weight at age 20 (quartiles)

[d] Limited to a sub-cohort of 264 cases and 106,272 non-cases with complete data on recalled weight at age 20

region (southern, western, northern Europe) based on UN geographical classification of countries, dietary patterns across EPIC countries (general consumption of plant, animal, and processed foods [34]), mean BMI, mean age at recruitment, percent 60 years or older at recruitment and percent ever HRT users among postmenopausal women.

Discussion

In this large prospective cohort study that had standardized direct measurements of anthropometry from over 220,000 women in nine European countries, we found very strong associations with endometrial cancer risk for both general obesity and fat distribution. Increased weight, BMI, waist circumference, WHR and adult weight gain were clearly associated with an increased risk of endometrial cancer. Of interest are the sub-group analyses that provided evidence for a particularly strong association among postmenopausal women, never HRT users and never OC users.

Our results of a two-fold increased risk, particularly among postmenopausal women, for a BMI greater than 30 and a three-fold risk increase for morbid obese women compared to normal weight women is corroborated by recently published studies that have shown risk increases ranging from 2 to up to 4.5 for women with a BMI over 30 [8, 10, 35–41]. In conjunction with the studies previously reviewed [1], there is now strong and consistent evidence that obesity increases risk of endometrial cancer. Our overall results support the possibility of a threshold effect of obesity, because the risk estimates were only slightly increased among overweight women (BMI ≥ 25– < 30 or waist circumference ≥80– < 88cm) but were substantially elevated among obese women (BMI ≥ 30 or waist circumference ≥88 cm). In younger women, it has been proposed that the influence of obesity on hormonal levels may occur only at higher levels of overweight [2], whereas among postmenopausal women, a more linear trend in risk may occur because adipose tissue directly influences estrogen levels [2]. In our investigation, we found evidence for a threshold effect in the postmenopausal women only; however, the small sample size of premenopausal women may have precluded observing this effect among these women. Most of these recent studies [8, 10, 35, 38, 41], but not all [36, 37], have found an increased risk among overweight women.

Height was not found to be a risk factor for endometrial cancer in our study. Only one [10] of the previous studies [8, 10, 35, 36, 39, 40] found height to increase risk. In that study, women over 175 cm had a 2.5-fold increased endometrial cancer risk as compared to women under 160 cm but no statistically significant trend across quintiles was observed [10].

Relatively few studies have examined the association of body fat distribution, as reflected by WHR and waist and hip circumference, and endometrial cancer risk and the results have been inconsistent. After adjustment for BMI, we found that waist but not hip circumference was associated with endometrial cancer risk in the total study population suggesting that upper body or abdominal fat is more etiologically relevant than lower body fat. WHR had an association independent of general obesity in five [4, 18, 19, 40, 42] of 10 [4, 5, 14–19, 40, 42] previous studies.

Table 4 Hazard ratio estimates of endometrial cancer by anthropometric factors, according to baseline menopausal status[a]

Anthropometric factor	Premenopausal (n = 91)			Postmenopausal (n = 376)		
	Number of cases[b]	Age- and center-stratified hazard ratios and 95% CI	Multivariate[c] hazard ratios and 95% CI	Number of cases[b]	Age- and center-stratified hazard ratios and 95% CI	Multivariate[c] hazard ratios and 95% CI
Weight (kg) in quartiles						
≤58.0	21	1.00	1.00	62	1.00	1.00
>58.0–<64.5	18	0.93 (0.49–1.76)	0.95 (0.50–1.81)	78	1.10 (0.79–1.54)	1.09 (0.78–1.53)
≥64.5–72.4	24	1.30 (0.71–2.38)	1.34 (0.72–2.48)	85	1.07 (0.76–1.49)	1.05 (0.75–1.48)
>72.4	28	1.63 (0.89–2.97)	1.57 (0.84–2.94)	151	1.82 (1.34–2.47)	1.81 (1.32–2.48)
p_{trend}		0.07	0.10		<0.0001	<0.0001
[d]HR per 5 kg	91	1.09 (1.01–1.19)	1.08 (0.99–1.18)	376	1.13 (1.08–1.17)	1.13 (1.08–1.17)
BMI categories (kg/m^2)						
<25	41	1.00	1.00	155	1.00	1.00
≥25–<30	33	1.49 (0.92–2.42)	1.53 (0.93–2.51)	120	1.04 (0.81–1.32)	1.04 (0.81–1.33)
≥30	17	1.61 (0.87–3.00)	1.55 (0.80–2.98)	101	1.95 (1.50–2.54)	1.96 (1.48–2.58)
p_{trend}		0.08	0.11		<0.0001	<0.0001
[d]HR per 1 kg/m^2	91	1.04 (1.00–1.09)	1.04 (0.99–1.09)	376	1.07 (1.05–1.09)	1.07 (1.05–1.10)
Waist circumference[b] (cm)						
<80	39	1.00	1.00	139	1.00	1.00
80–<88	23	1.64 (0.96–2.79)	1.73 (1.00–2.98)	77	1.02 (0.77–1.35)	1.04 (0.78–1.38)
≥88	26	2.06 (1.18–3.57)	2.09 (1.17–3.72)	145	1.83 (1.43–2.34)	1.90 (1.47–2.46)
p_{trend}		0.008	0.009		<0.0001	<0.0001
[d]HR per 5 cm	88	1.10 (1.00–1.22)	1.10 (0.99–1.22)	361	0.15 (1.10–1.20)	1.16 (1.11–1.22)
Hip circumference[b] in quartiles						
≤94.5	23	1.00	1.00	64	1.00	1.00
>94.5–<100.0	10	0.40 (0.19–0.85)	0.41 (0.19–0.86)	71	0.98 (0.70–1.38)	0.97 (0.69–1.36)
≥100.0–<106.0	27	1.09 (0.61–1.95)	1.11 (0.62–1.99)	73	0.87 (0.62–1.23)	0.84 (0.60–1.19)
≥106.0	28	1.12 (0.62–2.02)	1.09 (0.59–2.03)	154	1.78 (1.31–2.40)	1.75 (1.29–2.39)
p_{trend}		0.24	0.28		<0.0001	0.0001
[d]HR per 5 cm	88	1.10 (0.98–1.24)	1.09 (0.97–1.24)	362	1.18 (1.12–1.24)	1.18 (1.12–1.24)
Waist–hip ratio[b] in quartiles						
≤0.742	12	1.00	1.00	51	1.00	1.00
>0.742–<0.785	30	2.61 (1.33–5.15)	2.68 (1.35–5.31)	77	1.06 (0.74–1.52)	1.09 (0.76–1.56)
≥0.785–0.831	24	2.14 (1.04–4.38)	2.21 (1.07–4.56)	97	1.15 (0.81–1.62)	1.22 (0.86–1.72)
>0.831	22	2.25 (1.06–4.78)	2.13 (0.98–4.63)	136	1.43 (1.02–2.00)	1.55 (1.10–2.18)
p_{trend}		0.10	0.14		0.02	0.005
[d]HR per 0.1 unit	88	1.19 (0.88–1.60)	1.17 (0.86–1.60)	361	1.21 (1.05–1.40)	1.26 (1.09–1.46)

[a] Excludes 100 cases and 31,720 non-cases who were perimenopausal or with unknown menopausal status at baseline

[b] Totals and tests for trend exclude unknown values

[c] Stratified by age and center, and adjusted for total physical activity level, age at menarche, age at menopause (postmenopausal women), number of full-term pregnancies, age at birth of last child, ever use of oral contraceptives, ever use of hormone replacement therapy, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fiber intake, carbohydrate intake, and energy intake

[d] p-Values for interaction based on continuous measures in multivariate models were: 0.43 for weight, 0.29 for BMI, 0.12 for waist circumference, 0.47 for hip circumference, and 0.10 for waist–hip ratio

We found elevated risks of endometrial cancer with increasing general and abdominal obesity among both pre- and post-menopausal women, but the risk estimates for general obesity (weight and BMI) were greater and trends uniformly statistically significant for postmenopausal women. However, the sample size for premenopausal women was quite small (n = 91 cases) making it difficult to conclude with confidence that there are true differences in risks among pre- and post-menopausal women. Very few studies have examined the association between anthropometry and endometrial cancer risk separately for pre- and post-menopausal women. A few studies have found a somewhat stronger association among postmenopausal or older women [3, 43, 44] but one study noted a stronger association among younger women [35]. In pre-menopausal women, obesity may increase endometrial cancer risk by inducing chronic anovulation and progesterone deficiency [2]. At the time of menopause, when ovarian estrogen production ceases and the conversion of androgens to estrogens in adipose tissue becomes a major source of endogenous estrogens,

Table 5 Hazard ratio estimates of endometrial cancer by anthropometric factors, according to ever-use of hormone replacement therapy in postmenopausal women[a]

Anthropometric factor	Ever used hormone replacement therapy (n = 151)			Never used hormone replacement therapy (n = 186)		
	Number of cases[b]	Age- and center-stratified hazard ratios and 95% CI	Multivariate[c] hazard ratios and 95% CI	Number of cases	Age- and center-stratified hazard ratios and 95% CI	Multivariate[c] hazard ratios and 95% CI
Weight (kg) in quartiles						
≤58.0	32	1.00	1.00	27	1.00	1.00
>58.0–<64.5	37	1.06 (0.65–1.72)	1.08 (0.66–1.77)	33	1.06 (0.63–1.78)	1.06 (0.63–1.78)
≥64.5–72.4	29	0.73 (0.43–1.23)	0.75 (0.45–1.28)	45	1.26 (0.77–2.04)	1.28 (0.78–2.09)
>72.4	53	1.49 (0.94–2.38)	1.52 (0.94–2.45)	81	1.99 (1.27–3.12)	2.00 (1.25–3.18)
p_{trend}		0.16	0.15		0.0004	0.0006
[d]HR per 5 kg	151	1.05 (0.97–1.12)	1.04 (0.97–1.12)	186	1.18 (1.12–1.23)	1.18 (1.12–1.24)
BMI categories (kg/m^2)						
<25	79	1.00	1.00	62	1.00	1.00
≥25–<30	49	0.94 (0.65–1.36)	0.94 (0.64–1.37)	56	1.04 (0.72–1.50)	1.03 (0.71–1.51)
≥30	23	1.41 (0.87–2.28)	1.39 (0.84–2.30)	68	2.41 (1.67–3.47)	2.39 (1.62–3.53)
p_{trend}		0.35	0.38		<0.0001	<0.0001
[d]HR per 1 kg/m^2	151	1.02 (0.98–1.06)	1.02 (0.97–1.06)	186	1.10 (1.07–1.13)	1.10 (1.07–1.13)
Waist circumference[b] (cm)						
<80	77	1.00	1.00	52	1.00	1.00
80–<88	35	0.92 (0.61–1.38)	0.92 (0.61–1.39)	36	1.11 (0.72–1.71)	1.15 (0.74–1.79)
≥88	39	1.18 (0.78–1.78)	1.18 (0.77–1.80)	96	2.41 (1.68–3.45)	2.51 (1.72–3.64)
p_{trend}		0.53	0.54		<0.0001	<0.0001
[d]HR per 5 cm	151	1.05 (0.97–1.13)	1.05 (0.97–1.14)	184	1.22 (1.15–1.30)	1.23 (1.16–1.31)
Hip circumference[b] in quartiles						
≤94.5	36	1.00	1.00	24	1.00	1.00
>94.5–<100.0	34	0.85 (0.53–1.36)	0.85 (0.52–1.37)	30	0.99 (0.58–1.70)	0.97 (0.56–1.66)
≥100.0–<106.0	30	0.64 (0.39–1.05)	0.61 (0.37–1.00)	40	1.08 (0.65–1.81)	1.07 (0.64–1.80)
≥106.0	51	1.32 (0.84–2.06)	1.29 (0.81–2.05)	91	2.10 (1.32–3.34)	2.04 (1.26–3.29)
p_{trend}		0.34	0.44		0.0001	0.0003
[d]HR per 5 cm	151	1.06 (0.97–1.17)	1.06 (0.96–1.17)	185	1.23 (1.15–1.32)	1.23 (1.15–1.32)
Waist–hip ratio[b] in quartiles						
≤0.742	26	1.00	1.00	19	1.00	1.00
>0.742–<0.785	40	1.13 (0.69–1.87)	1.20 (0.73–1.98)	32	1.16 (0.66–2.06)	1.17 (0.66–2.09)
≥0.785–0.831	41	1.17 (0.71–1.93)	1.25 (0.75–2.07)	48	1.29 (0.75–2.22)	1.38 (0.80–2.39)
>0.831	44	1.26 (0.76–2.09)	1.36 (0.81–2.29)	85	1.79 (1.07–2.99)	1.88 (1.11–3.19)
p_{trend}		0.38	0.25		0.008	0.005
[d]HR per 0.1 unit	151	1.05 (0.83–1.34)	1.09 (0.85–1.40)	184	1.37 (1.14–1.66)	1.40 (1.15–1.70)

[a] Excludes 39 cases and 8,804 non-cases with missing hormone replacement therapy data

[b] Totals and tests for trend exclude unknown values

[c] Stratified by age and center, and adjusted for total physical activity level, age at menarche, age at menopause, number of full-term pregnancies, age at birth of last child, ever use of oral contraceptives, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fiber intake, carbohydrate intake, and energy intake

[d] p-Values for interaction based on continuous measures in multivariate models were: 0.01 for weight, 0.002 for BMI, 0.004 for waist circumference, 0.02 for hip circumference, and 0.08 for waist–hip ratio

excess body fat can directly result in increased total and bioavailable estrogens [2]. In addition, decreased serum levels of sex hormone binding globulin occur with obesity, that result in increased levels of bioavailable estrogens that are unopposed by progesterones after menopause [2]. In this hormonal milieu, proliferation of epithelial tissue in the endometrium is increased, as are somatic mutations and replication errors that can result in endometrial cancer [45].

The subgroup analyses of effect modification by HRT and OC use provided interesting results that have not been studied in detail previously. We observed 2- to 2.5-fold increased risks for all anthropometric factors considered among never HRT users, while ever-users had much lower and non-statistically significant increased risks for these factors. These results are consistent with a large cohort study of HRT use among postmenopausal women [20] that also found obesity increases endometrial cancer risk more strongly in never-users than in ever-users of HRT. In that study [20], obesity (BMI ≥ 30; compared to BMI < 25) was associated with a four-fold increase in

Table 6 Hazard ratio estimates of endometrial cancer by anthropometric factors, according to ever-use of oral contraceptives in all women[a]

Anthropometric factor	Ever used oral contraceptives (n = 215)			Never used oral contraceptives (n = 315)		
	Number of cases[b]	Age- and center-stratified hazard ratios and 95% CI	Multivariate[c] hazard ratios and 95% CI	Number of cases	Age- and center-stratified hazard ratios and 95% CI	Multivariate[c] hazard ratios and 95% CI
Weight (kg) in quartiles						
≤58.0	49	1.00	1.00	51	1.00	1.00
>58.0–<64.5	53	1.07 (0.72–1.59)	1.08 (0.72–1.60)	58	1.02 (0.70–1.49)	1.02 (0.70–1.50)
≥64.5–72.4	40	0.80 (0.52–1.24)	0.80 (0.52–1.24)	76	1.17 (0.81–1.68)	1.19 (0.82–1.71)
>72.4	73	1.59 (1.08–2.34)	1.56 (1.05–2.32)	130	1.80 (1.28–2.52)	1.83 (1.29–2.58)
p_{trend}		0.04	0.06		<0.0001	<0.0001
[d]HR per 5 kg	215	1.08 (1.03–1.15)	1.08 (1.02–1.14)	315	1.12 (1.08–1.17)	1.13 (1.08–1.18)
BMI categories (kg/m^2)						
<25	114	1.00	1.00	116	1.00	1.00
≥25–<30	62	0.96 (0.70–1.33)	0.98 (0.70–1.35)	106	1.15 (0.88–1.51)	1.16 (0.88–1.53)
≥30	39	1.74 (1.19–2.53)	1.71 (1.15–2.54)	93	1.90 (1.42–2.55)	1.94 (1.43–2.63)
p_{trend}		0.03	0.04		<0.0001	<0.0001
[d]HR per 1 kg/m^2	215	1.05 (1.02–1.08)	1.05 (1.01–1.08)	315	1.07 (1.04–1.09)	1.07 (1.05–1.09)
Waist circumference[b] (cm)						
<80	118	1.00	1.00	106	1.00	1.00
80–<88	35	0.72 (0.49–1.06)	0.75 (0.51–1.10)	80	1.39 (1.03–1.87)	1.44 (1.07–1.94)
≥88	61	1.44 (1.04–1.99)	1.47 (1.05–2.07)	128	1.90 (1.44–2.51)	1.97 (1.48–2.63)
p_{trend}		0.09	0.08		<0.0001	<0.0001
[d]HR per 5 cm	214	1.08 (1.01–1.15)	1.08 (1.01–1.16)	314	1.14 (1.08–1.19)	1.15 (1.09–1.21)
Hip circumference[b] in quartiles						
≤94.5	54	1.00	1.00	55	1.00	1.00
>94.5–<100.0	46	0.78 (0.52–1.16)	0.78 (0.52–1.16)	52	0.88 (0.60–1.29)	0.88 (0.60–1.29)
≥100.0–<106.0	48	0.81 (0.55–1.21)	0.82 (0.54–1.22)	69	0.97 (0.68–1.40)	0.96 (0.67–1.39)
≥106.0	66	1.28 (0.88–1.86)	1.27 (0.86–1.87)	139	1.67 (1.20–2.32)	1.69 (1.21–2.37)
p_{trend}		0.17	0.20		0.0002	0.0003
[d]HR per 5 cm	214	1.10 (1.02–1.18)	1.09 (1.01–1.18)	315	1.17 (1.11–1.23)	1.18 (1.12–1.24)
Waist–hip ratio[b] in quartiles						
≤0.742	35	1.00	1.00	43	1.00	1.00
>0.742–<0.785	63	1.51 (1.00–2.30)	1.54 (1.01–2.35)	67	1.16 (0.79–1.71)	1.15 (0.78–1.70)
≥0.785–0.831	62	1.46 (0.96–2.23)	1.51 (0.98–2.31)	84	1.21 (0.83–1.76)	1.23 (0.84–1.80)
>0.831	54	1.45 (0.93–2.25)	1.52 (0.97–2.39)	120	1.49 (1.03–2.16)	1.54 (1.06–2.25)
p_{trend}		0.18	0.12		0.02	0.02
[d]HR per 0.1 unit	214	1.09 (0.90–1.32)	1.10 (0.91–1.33)	314	1.17 (1.00–1.38)	1.20 (1.01–1.42)

[a] Excludes 37 cases and 13,277 non-cases with missing oral contraceptive data

[b] Totals and tests for trend exclude unknown values

[c] Stratified by age and center, and adjusted for total physical activity level, age at menarche, menopausal status, age at menopause, number of full-term pregnancies, age at birth of last child, ever use of hormone replacement therapy, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fiber intake, carbohydrate intake, and energy intake

[d] p-Values for interaction based on continuous measures in multivariate models were: 0.09 for weight, 0.16 for BMI, 0.17 for waist circumference, 0.09 for hip circumference, and 0.66 for waist–hip ratio

risk in never-users but only a slightly increased risk among ever-users of HRT. Conversely, one previous study reported a possible additive effect of estrogen replacement therapy and body weight on endometrial cancer risk, but this study had low power to detect interactions [21]. Another study [8], found a statistically significant interaction between HRT use and weight gain as a continuous linear variable, however they did not see a clear difference in the association of BMI or weight gain categories with endometrial cancer risk when they stratified by never, former, and current HRT use. The biologic mechanism for an interaction between obesity, HRT, and endometrial cancer risk is unclear but may be related to the presence of progestins in the exogenous therapy that counterbalance the mitogenic effects of endogenous estrogens produced in the adipose tissue [2, 20]. It is also possible that exogenous estrogens in HRT elevate circulating estrogen levels to such an extent that increasing levels of endogenous estrogens due to obesity have little

additional effect [20]. This hypothesis is supported by our results. The biologic plausibility of our findings is further supported by consistent reports that HRT use modifies the obesity–breast cancer association in a similar way [46]. Previous research has demonstrated markedly varying associations with endometrial cancer risk according to different formulations of HRT with endometrial cancer risk [2, 20]. We were unable, in this study, to examine the associations for specific types of HRT since this information is currently unavailable in EPIC. However, we found in our cohort that HRT use increased risk of endometrial cancer for all categories of BMI examined including normal weight women.

In a comparable analysis of effect modification by OC use, we also noted stronger associations of body measures among the never OC users than among the ever OC users. One other study has previously examined the interaction between BMI and OC use but did not find a statistically significant interaction [10]. The use of estrogen–progestin combination type of OCs has been shown to decrease risk of endometrial cancer or not to affect risk [2, 45]. Women who were currently using or had previously used OCs may have benefitted from the protective effect of progestins in the OCs especially when they were overweight or obese. Since no other studies have found an interaction between anthropometric factors and OC use, this finding needs further investigation.

There is mounting evidence that adult weight gain increases endometrial cancer risk. Our results of a 75% increase in risk for women who gained more than 20 kg since age 20 are supported by most [3–6, 8–10, 36, 40], though not all [7, 11–13], previous studies that have examined some aspect of lifetime weight changes. Moreover, recent BMI rather than BMI or weight at early adulthood was found to be predictive of risk in our study (data not shown) consistent with other investigations [3, 5, 8, 11, 12, 47]. Only three studies, thus far, have found an increased endometrial cancer risk for women who were overweight at young ages [7, 41, 48]. Xu and colleagues [41] proposed that adolescent adiposity is not a major risk factor unless it is combined with adult weight gain later in life. We examined this question and found that women who were overweight or obese at age 20 had an increased risk of endometrial cancer only if their adult weight gain exceeded 15 kg. Xu et al. [41] observed that weight gain particularly during the perimenopausal period was particularly predictive of an increased risk.

This study had several strengths and a few caveats that need to be considered. The cohort is heterogeneous, large, multinational, and representative of different regions of Europe. The study methods were standardized across the study centers with measurements of anthropometry taken directly by the study personnel on all participants with the exception of the health conscious UK cohort, but for this group the self-reported data were corrected for measurement error. A full investigation of confounding and effect modification was undertaken. Weight at age 20 was measured by recall only. Although past adult weight has been shown to be reliably recalled [8], the accuracy of recall may be influenced by other factors including current weight [49].

Although full data were available on baseline exposures, data on exposures during follow-up were unavailable, including change in menopausal status or subsequent use of HRT or OCs. Hence, we were unable to adjust for changes in exposures that may have occurred during the six-year follow-up period. For menopausal status, nearly 40% of the cohort in this analysis were premenopausal at baseline, therefore, some of these women were likely to be perimenopausal or postmenopausal at the time of diagnosis. Although some heterogeneity was found across the sub-cohorts for BMI, none of the country-related or individual-related variables that were investigated explained the heterogeneity observed. Since the other anthropometric factors examined were not heterogeneous and the country-specific risk estimates were very similar and in the same direction, this heterogeneity for BMI may have occurred by chance.

In conclusion, we found clear evidence that increased general obesity, abdominal adiposity, and adult weight gain were strong risk factors for endometrial cancer. We also found that the association between body measures and risk may vary according to menopausal status, HRT and OC use, with the greatest risks for postmenopausal women, never HRT and never OC users. The findings of possible effect modification by these factors will require additional confirmation in future studies. This study provides strong evidence to support public health recommendations for weight control. Furthermore, it has highlighted population sub-groups who may be at particularly increased risk and for whom specific surveillance would be appropriate.

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