Metabolically Defined Body Size Phenotypes and Risk of Endometrial Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)

Nathalie Kliemann[1], Romain Ould Ammar[1], Carine Biessy[1], Audrey Gicquiau[1], Verena Katzke[2], Rudolf Kaaks[2], Anne Tjønneland[3,4], Anja Olsen[4,5], Maria-Jose Sánchez[6,7,8,9], Marta Crous-Bou[10,11], Fabrizio Pasanisi[12], Sandar Tin Tin[13], Aurora Perez-Cornago[13], Dagfinn Aune[14,15,16], Sofia Christakoudi[14,17], Alicia K. Heath[14], Sandra M. Colorado-Yohar[8,18,19], Sara Grioni[20], Guri Skeie[21], Hanna Sartor[22], Annika Idahl[23], Charlotta Rylander[21], Anne M. May[24], Elisabete Weiderpass[1], Heinz Freisling[1], Mary C. Playdon[25,26], Sabina Rinaldi[1], Neil Murphy[1], Inge Huybrechts[1], Laure Dossus[1], and Marc J. Gunter[1]

ABSTRACT

Background: Obesity is a risk factor for endometrial cancer but whether metabolic dysfunction is associated with endometrial cancer independent of body size is not known.

Methods: The association of metabolically defined body size phenotypes with endometrial cancer risk was investigated in a nested case–control study (817 cases/ 817 controls) within the European Prospective Investigation into Cancer and Nutrition (EPIC). Concentrations of C-peptide were used to define metabolically healthy (MH; <1st tertile) and metabolically unhealthy (MU; ≥1st tertile) status among the control participants. These metabolic health definitions were combined with normal weight (NW); body mass index (BMI)<25 kg/m^2 or waist circumference (WC)<80 cm or waist-to-hip ratio (WHR)<0.8) and overweight (OW; BMI≥25 kg/m^2 or WC≥80 cm or WHR≥0.8) status, generating four phenotype groups for each anthropometric measure: (i) MH/NW, (ii) MH/OW, (iii) MU/NW, and (iv) MU/OW.

Results: In a multivariable-adjusted conditional logistic regression model, compared with MH/NW individuals, endometrial cancer risk was higher among those classified as MU/NW [OR_{WC}, 1.48; 95% confidence interval (CI), 1.05–2.10 and OR_{WHR}, 1.68; 95% CI, 1.21–2.35] and MU/OW (OR_{BMI}, 2.38; 95% CI, 1.73–3.27; OR_{WC}, 2.69; 95% CI, 1.92–3.77 and OR_{WHR}, 1.83; 95% CI, 1.32–2.54). MH/OW individuals were also at increased endometrial cancer risk compared with MH/NW individuals (OR_{WC}, 1.94; 95% CI, 1.24–3.04).

Conclusions: Women with metabolic dysfunction appear to have higher risk of endometrial cancer regardless of their body size. However, OW status raises endometrial cancer risk even among women with lower insulin levels, suggesting that obesity-related pathways are relevant for the development of this cancer beyond insulin.

Impact: Classifying women by metabolic health may be of greater utility in identifying those at higher risk for endometrial cancer than anthropometry *per se*.

Introduction

Endometrial cancer is the second most common gynecological cancer worldwide, with 604,127 new cases and 341,831 deaths reported in 2020 (1). Higher body mass index (BMI≥25 kg/m^2) is a well-established risk factor for endometrial cancer (2–5). A meta-analysis of prospective studies has shown that every 5 kg/m^2 increase in BMI is associated with a 60% increase in endometrial

[1]International Agency for Research on Cancer, Lyon, France. [2]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. [3]Danish Cancer Society Research Center, Copenhagen, Denmark. [4]Department of Public Health, University of Copenhagen, Copenhagen, Denmark. [5]Department of Public Health, Aarhus University, Aarhus, Denmark. [6]Escuela Andaluza de Salud Pública (EASP), Granada, Spain. [7]Instituto de Investigación Biosanitaria ibs, GRANADA, Granada, Spain. [8]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. [9]Department of Preventive Medicine and Public Health, University of Granada, Granada, Spain. [10]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO)—Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain. [11]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [12]Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy. [13]Nuffield Department of Population Health, Cancer Epidemiology Unit, University of Oxford, Oxford, England. [14]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom. [15]Department of Nutrition, Oslo New University College, Oslo, Norway. [16]Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway. [17]Department of Inflammation Biology, King's College London, London, United Kingdom. [18]Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain. [19]Research Group on Demography and Health, National Faculty of Public Health, University of Antioquia, Medellín, Colombia. [20]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy. [21]Department of Community Medicine, UIT—The Arctic University of Norway, Tromsø, Norway. [22]Diagnostic Radiology, Lund University, Lund, Sweden. [23]Department of Clinical Sciences, Obstetrics and Gynecology, Umeå University, Umeå, Sweden. [24]Julius Center for Health Sciences and Primary care, University Medical Center Utrecht, Utrecht, the Netherlands. [25]Department of Nutrition and Integrative Physiology, University of Utah, Salt Lake City, Utah. [26]Cancer Control and Population Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Marc J. Gunter, International Agency for Research on Cancer, World Health Organization, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France. Phone: 334-727-3814; E-mail: GunterM@iarc.fr

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cancer risk (6). Recently, several studies have also shown that waist circumference (WC) and waist-to-hip ratio (WHR), both indicators of central adiposity, may be associated with endometrial cancer risk independently of BMI (7, 8). Potential biological mechanisms linking obesity with endometrial cancer development include alterations in the metabolism of endogenous hormones, such as sex steroids, insulin, and inflammation (9–11).

Hyperinsulinemia, a condition characterized by elevated levels of insulin in the fasting state, has been positively associated with endometrial cancer risk in several prospective studies (12, 13), and in a Mendelian randomization analysis (5). C-peptide, a marker for pancreatic insulin secretion, has also generally been associated with endometrial cancer risk (12, 14). Mechanistically, insulin may promote endometrial cancer development through direct mitogenic effects on the growth of endometrial cells, and indirectly via sex hormone disruption (15, 16).

Metabolic dysfunction has been associated with a number of adverse health outcomes independent of BMI (17–26). Indeed, over a third of adults in the normal weight (NW) range may have metabolic dysfunction that puts them at elevated cardiometabolic disease risk (27). Accumulating evidence suggests that individuals with metabolic dysfunction, either in the NW or overweight (OW)/obese BMI range, are at greater risk of developing colorectal, breast, pancreatic, prostate and bladder cancers, compared with subjects who are metabolically healthy (MH; refs. 17, 18, 24, 25, 28). However, whether metabolic dysregulation also raises endometrial cancer risk independent of obesity is less clear. A study conducted within the Framingham Heart Study found that metabolic dysregulation (based on elevated blood glucose) was associated with higher risk of endometrial cancer among women with OW and obesity, but not among women within the normal range of BMI and WHR (20). However, another study in the SEER-Medicare–linked database found that metabolic syndrome (comprised of having three or more parameters out of clinical range, including central obesity, fasting glucose, blood pressure, and triglycerides) remained associated with endometrial cancer even after adjusting for level of obesity (29). However, to our knowledge no studies have specifically evaluated hyperinsulinemia in relation to endometrial cancer according to body size in a large-scale prospective cohort.

To address these current gaps in the literature, we conducted an investigation of metabolically defined body size phenotypes (based on C-peptide levels combined with anthropometric measures) and their association with endometrial cancer risk in a nested case–control study within the European Prospective Investigation into Cancer and Nutrition (EPIC).

Materials and Methods

Study population

EPIC is an ongoing multicenter prospective cohort study designed to assess the relationship between diet, lifestyle, and genetic and metabolic factors with cancer and other chronic diseases. A detailed description of the cohort has been published elsewhere (30, 31). In summary, a total of 521,324 participants (~70% female) were recruited between 1992 and 2000 from 23 centers across 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). Written informed consent was provided by all participants. The study was in accordance with human subjects' protection principles (Declaration of Helsinki) and was approved by the ethical review boards from the International Agency for Research on Cancer (IARC) and from all local centers.

Follow-up and ascertainment of endometrial cancer

Incident endometrial cancer cases were identified using cancer registries in Norway, United Kingdom, Spain, Italy, and the Netherlands and using a combination of sources such as active follow-up of study subjects, cancer and pathology registries, and health insurance records in France and Germany. The collection and standardization of clinical and pathological data on each cancer site were performed following a detailed protocol. The end of follow-up was established as the latest date of follow-up for cancer incidence, death or end of follow-up, whichever came first. Censoring dates for complete follow-up from cancer registries were between December 2009 and December 2013. Endometrial cancer cases (C540–549) were identified using the 10th Revision of the International Classification of Diseases ICD-10) and the 3rd Revision of the International Classification of Diseases for Oncology (ICD-O-3). Endometrial cancer type 1 histologies included endometrioid adenocarcinoma, adenosquamous carcinoma, adenocarcinoma with squamous metaplasia, adenocarcinoma not otherwise specified, adenocarcinoma in adenomatous polyp, mucinous adenocarcinoma, mucin-producing adenocarcinoma (codes 8380, 8560, 8570, 8140, 8210, 8480, and 8481). The inclusion of adenocarcinoma not otherwise specified in Type 1 is justified because endometrioid adenocarcinoma is the most common type of adenocarcinoma. Type 2 histologies included squamous cell carcinoma, clear cell adenocarcinoma, mixed cell adenocarcinoma, serous cystadenocarcinoma, papillary serous cystadenocarcinoma (codes 8070, 8310, 8323, 8441, and 8460). Other histologies were not classified into either type (codes 8000, 8010, 8020, 8260, 8950, and 8980).

Selection of case and control subjects

Incident endometrial cancer cases were identified after the baseline blood collection and before the end of the follow up in each study center. Women who had a previous cancer or had undergone hysterectomy at the time of blood collection were excluded. For each case, one control participant was randomly chosen from the overall EPIC cohort of women who were free of cancer at the time of diagnosis of the index case. An incidence density sampling protocol for control selection was used, such that controls could include participants who became a case later in time, whereas each control could also be sampled more than once. The matching factors for cases and controls were study center, fasting status, age at blood collection, time of day at blood collection (±4 h), menopausal status, exogenous hormone use and phase of menstrual cycle at blood collection.

Laboratory measurements

Blood samples were collected at baseline according to standardized procedures and stored in the central EPIC biorepository at IARC (−196°C, liquid nitrogen) for all countries included in this study. C-peptide was measured in two phases. In the first phase, 378 serum samples were measured by an immunoradiometric assay (Immunotech), with intrabatch coefficients of variation (CV) <3% and interbatch CVs <11% for a C-peptide concentration of 0.50 nmol/L (14). In the second phase, 1,256 plasma samples were measured by an ELISA assay (Mercodia) with intrabatch CV <7% and interbatch CVs <6% for a C-peptide concentration of 0.66 nmol/l (32). All measurements were performed in the immunoassay laboratory at IARC. Samples from matched case–control sets were assayed in the same analytical batch. Laboratory personnel were blinded to case–control status of the samples. Concentrations of C-peptide for cases and controls by method of analysis are presented in Supplementary Table S1.

Assessment of anthropometric, lifestyle, and dietary exposures

All participants underwent assessment of anthropometrics, lifestyle, dietary intake, medical history, and demographics at baseline. Standard protocols for the measurement of body weight and height were used in all centers, except for Oxford, and Norway where these were self-reported. However, previous studies have shown these self-reported anthropometric measures are valid for identifying associations in epidemiological studies (33, 34). Assessed weight and height were used to calculate BMI (kg/m^2). WC was measured either at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest. WC was divided by hip circumference to generate the WHR. Lifestyle and medical history self-reported questionnaires collected information on education, smoking status, alcohol consumption, and physical activity level, diabetes, and reproductive history (menopausal status, oral contraceptive use, menopausal hormone use, age at menarche and menopause, and age and number of full-term pregnancies). The validated Cambridge physical activity index was used to classify past-year physical activity levels in occupational, leisure, and household domains (35). Validated country/center-specific dietary questionnaires were used to obtain information on dietary intake. Different types of dietary questionnaires were used in each study center, including semiquantitative food frequency questionnaires (FFQ) with or without an estimation of individual average portion size and diet history questionnaires combining a FFQ and 7-day dietary recalls (30, 31).

Metabolically defined body size phenotype definitions

Concentrations of C-peptide among the control population were used to define metabolic health status. Individuals were classified as MH if below the first tertile (Supplementary Table S2) or metabolically unhealthy (MU) if above the first tertile. This definition of metabolic health was derived given that the risk of endometrial cancer was elevated in women in the 2nd and 3rd tertiles of C-peptide compared with those in the 1st tertile (Supplementary Table S3). In addition, the same procedure was performed using quartiles (1st quartile as MH) and median values (<median as MH) of C-peptide standardized concentration amongst the control population (Supplementary Table S2).

These metabolic health definitions were then combined with NW (BMI<25 kg/m^2 or WC< 80 cm or WHR< 0.8) and OW (BMI≥25 kg/m^2 or WC≥ 80 cm or WHR≥ 0.8) status, generating four phenotype groups for each of the three anthropometric measures separately (in total 12 groups; 4×3): MH/NM; MH/OW; MU/NW; and MU/OW. The WC and WHR cutoff points were based on those from the International Diabetes Federation (36), which are gender and ethnic-specific cutoff points for European populations.

Statistical analysis

Descriptive analyses were performed and differences between cases and controls were assessed using paired sample *t* test for continuous variables and paired χ^2 test for categorical variables. Descriptive analyses were also performed between metabolically defined body size phenotype groups among the controls. As C-peptide was measured in two phases (in 2007 and then in 2019), standardized values were used in the analysis. The standardization was done by phase of the measurements, with all features following the reduced, centered normal distribution (mean = 0 and SD = 1). Partial Pearson correlations in the control group adjusted for batch and age at blood collection, between levels of C-peptide and anthropometrics variables were computed (Supplementary Table S4). Conditional logistic regression, stratified by case–control set, was used to compute odds ratios (OR) and 95% confidence intervals (CI) for the associations between metabolically defined body size phenotypes and endometrial cancer. The MH/NW was used as the reference category. The basic model was built on matching factors only, whereas the adjusted model was built on matching factors and a list of known risk factors for endometrial cancer that can potentially act as confounders, including: age at menopause (age at menopause <50; ≥ 50 years; missing), age at menarche (continuous), parity (0; 1; 2; >2; missing), hormone use (yes; no; missing), physical activity index (inactive; moderately inactive; moderately active; active; missing), smoking status (never; former smoker and current smoker; unknown), educational level (primary/no schooling; technical/professional/secondary and longer education; missing), total energy intake (continuous), alcohol intake (continuous), height (continuous), and diabetes (yes; no; missing). A separate model, including only OW participants and with the MU/OW category as reference, was also run. As sensitivity analyses, all models were rerun using the phenotypes defined on the basis of quartiles or on median level of C-peptide cutoff points. Also, analyses were repeated considering only the upper tertile as MU. Sensitivity analyses were also performed among postmenopausal women only; among non-exogenous hormone users only; among fasting participants only; among endometrial cancer type 1 only (defined by histology as explained in case ascertainment section); and among individuals from phase 2 only (as explained in laboratory measurements section). Furthermore, sensitivity analyses were conducted excluding cases diagnosed within the first 2 years of follow-up and their matched controls and excluding participants with diabetes. Statistical tests used in the analysis were all two-sided, and a *P* value of <0.05 was considered statistically significant. Analyses were conducted using SAS software.

Data availability

EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centers. The primary responsibility for accessing the data belongs to IARC and the EPIC centers. Access to materials from the EPIC study can be requested by contacting epic@iarc.fr.

Results

The current analysis used data from 1,634 women who were included in a nested case–control study with available C-peptide levels. A total of 817 women were classified as incident endometrial cancer cases and 817 were classified as matched controls. Among the cases, a total of 728 women were classified as type 1, 40 women were classified as type 2, and 49 women had unknown tumor type.

Table 1 shows that endometrial cancer cases had older age at menopause, but younger age at first menstrual period and lower number of full-term pregnancies than the controls. Endometrial cancer cases also had higher levels of C-peptide and greater BMI and WC than controls. In line with this, a higher proportion of control participants were classified as MH/NW and MH/OW compared with cases considering all anthropometric cutoff points. The baseline characteristics of the control group participants by metabolically defined body size phenotypes are shown in **Table 2**. Compared with the MH/NW group and considering the BMI classification, a greater proportion of MU/NW control participants reported having longer

Table 1. Baseline characteristics of participants in a nested case–control study within EPIC.

Baseline characteristics	Endometrial Cancer Controls ($N = 817$) Mean (SD) or N (%)	Cases ($N = 817$) Mean (SD) or N (%)	P[a]
C-peptide (ng/mL)[g]	1.89 (1.22)	2.14 (1.43)	<0.0001
Height (cm)	161.0 (7.0)	160.7 (6.8)	0.34
Body mass index (kg/m^2)	25.7 (4.1)	27.7 (5.3)	<0.0001
Waist circumference (cm)	81.3 (10.5)	85.3 (12.4)	<0.0001
Waist/hip ratio (cm/cm)	0.8 (0.1)	0.8 (0.1)	0.05
Age at blood collection (years)	54.8 (7.6)	54.8 (7.6)	0.44
Fasting status at blood collection			0.99
Not fasting	366 (44.8%)	367 (44.9%)	
In between	148 (18.1%)	146 (17.9%)	
Fasting	303 (37.1%)	304 (37.2%)	
Age at menopause (years)	49.6 (4.3)	50.9 (4.0)	<0.0001
Age at first menstrual period (years)	13.1 (1.6)	12.9 (1.5)	0.0017
Full-term pregnancy			0.0034
Yes	707 (87.9%)	660 (82.8%)	
Number of full-term pregnancies[b]	2.4 (1.1)	2.3 (1.0)	0.02
Age at first full-term pregnancy (years)[b]	25.2 (4.2)	25.1 (4.1)	0.76
Menopausal status at blood collection			NA
Premenopausal	206 (25.2)	206 (25.2)	
Postmenopausal + Surgical postmen (bilateral ovariectomy)	496 (60.7)	496 (60.7)	
Perimenopausal	115 (14.1)	115 (14.1)	
Use of pill/HRT at blood collection			NA
No	650 (81.0)	650 (81.0)	
Yes	152 (19.0)	152 (19.0)	
Educational level			0.14
Primary/no schooling	365 (46.6%)	337 (43.4%)	
Technical/professional/secondary	277 (35.4%)	310 (39.9%)	
Longer education	141 (18.0%)	129 (16.6%)	
Physical activity			0.15
Inactive	201 (24.6%)	235 (28.8%)	
Moderately inactive	304 (37.2%)	270 (33.0%)	
Moderately active	190 (23.3%)	178 (21.8%)	
Active	108 (13.2%)	113 (13.8%)	
Smoking status			0.11
Never	495 (60.6%)	516 (63.2%)	
Former smoker	167 (20.4%)	173 (21.2%)	
Current smoker	138 (16.9%)	108 (13.2%)	
Diabetes			0.25
Yes	24 (3.4%)	32 (4.5%)	
Alcohol intake (g/d)[h]	7.2 (10.5)	6.6 (9.8)	0.32
Total energy intake (kcal/d)	1,918.3 (531.8)	1,905.7 (591.7)	0.6
Metabolic health/BMI definition			<0.0001
Metabolically healthy/normal weight[c]	179 (21.9%)	121 (14.8%)	
Metabolically healthy/overweight[d]	94 (11.5%)	81 (9.9%)	
Metabolically unhealthy/normal weight[e]	228 (27.9%)	166 (20.3%)	
Metabolically unhealthy/overweight[f]	316 (38.7%)	449 (55.0%)	
Metabolic health/WC definition			<0.0001
Metabolically healthy/normal weight[c]	180 (23.7%)	110 (14.5%)	
Metabolically healthy/overweight[d]	84 (11.1%)	83 (10.9%)	
Metabolically unhealthy/normal weight[e]	205 (27.0%)	169 (22.3%)	
Metabolically unhealthy/overweight[f]	290 (38.2%)	397 (52.3%)	
Metabolic health/WHR definition			0.0006
Metabolically healthy/normal weight[c]	173 (22.8%)	125 (16.5%)	
Metabolically healthy/overweight[d]	91 (12.0%)	68 (9.0%)	
Metabolically unhealthy/normal weight[e]	207 (27.3%)	225 (29.6%)	
Metabolically unhealthy/overweight[f]	288 (37.9%)	341 (44.9%)	

Abbreviations: BMI, body mass index; HRT, hormone replacement therapy; NA, Not applicable because was used as a matching factor; WC, waist circumference; WHR, waist-to-hip ratio.

[a]Paired sample t test for continuous variable and paired χ^2test for categorical variables.

[b]Among parous women.

[c]Metabolically healthy/normal weight (BMI < 25 kg/m^2 or waist circumference <80 cm or waist-to-hip ratio <0.8) plus below tertile 1 of C-peptide.

[d]Metabolically healthy/overweight (BMI ≥ 25 kg/m^2, or waist circumference ≥80 cm or waist-to-hip ratio ≥0.8), plus below tertile 1 of C-peptide.

[e]Metabolically unhealthy/normal weight (BMI < 25 kg/m^2 or waist circumference <80 cm or waist-to-hip ratio <0.8), plus above tertile 1 of C-peptide.

[f]Metabolically unhealthy/overweight (BMI ≥ 25 kg/m^2, or waist circumference ≥80 cm or Waist-to-hip ratio ≥0.8), plus above tertile 1 of C-peptide.

[g]Median (Interquartile range) among controls: 1.57 (1.05–2.32) and cases: 1.75 (1.16–2.64).

[h]Median (Interquartile range) among controls: 2.5 (0.3–10.8) and cases: 2.1 (0.2–9.3).

Table 2. Baseline characteristics of control group participants by metabolic health (hyperinsulinemia)–defined body size phenotypes using anthropometric cutoff points in the EPIC.

Baseline characteristics	Metabolic health/BMI definition ($N = 1,634$) Metabolically healthy NW[d]	OW/OB[e]	Metabolically unhealthy NW[f]	OW/OB[g]	P	Metabolic health/WC definition ($N = 1,518$) Metabolically healthy NW[d]	OW/OB[e]	Metabolically unhealthy NW[f]	OW/OB[g]	P	Metabolic health/WHR definition ($N = 1,518$) Metabolically healthy NW[d]	OW/OB[e]	Metabolically unhealthy NW[f]	OW/OB[g]	P
N	**300**	175	394	765		290	167	374	687		298	159	432	629	
Age at blood collection (y)[a]	53.2 (8.0)	54.5 (6.9)	54.6 (7.9)	55.6 (7.3)	<0.001	52.9 (7.7)	55.1 (7.6)	54.2 (8.0)	56.2 (7.5)	<0.001	52.9 (7.8)	55.3 (7.3)	54.5 (8.0)	56.1 (7.5)	<0.001
Fasting status[b]					<0.001					<0.001					<0.001
Not fasting	73 (24.3)	34 (19.4)	268 (68.0)	358 (46.8)		67 (23.1)	31 (18.6)	238 (63.6)	311 (45.3)		70 (23.5)	28 (17.6)	277 (64.1)	272 (43.2)	
In between	60 (20.0)	38 (21.7)	65 (16.5)	131 (17.1)		59 (20.3)	30 (18.0)	58 (15.5)	117 (17.0)		62 (20.8)	27 (17.0)	63 (14.6)	112 (17.8)	
Fasting	167 (55.7)	103 (58.9)	61 (15.5)	276 (36.1)		164 (56.6)	106 (63.5)	78 (20.9)	259 (37.7)		166 (55.7)	104 (65.4)	92 (21.3)	245 (39.0)	
Age at menopause (y)[a]	50.4 (3.8)	49.7 (4.6)	50.2 (4.0)	50.3 (4.3)	0.67	50.1 (3.7)	50.3 (4.7)	50.1 (4.0)	50.5 (4.3)	0.64	50.0 (4.3)	50.4 (4.0)	50.2 (4.2)	50.5 (4.3)	0.80
Age at 1st menstrual period (y)[a]	13.1 (1.6)	12.9 (1.8)	13.2 (1.5)	12.8 (1.5)	0.007	13.1 (1.6)	12.9 (1.8)	13.0 (1.5)	12.9 (1.6)	0.37	12.9 (1.6)	13.1 (1.8)	12.9 (1.6)	13.0 (1.6)	0.47
Full-term pregnancy[b]															
Yes	245 (83.6)	143 (83.6)	322 (83.4)	657 (87.5)	0.17	239 (85.1)	134 (81.2)	298 (82.3)	593 (87.6)	0.06	239 (83.0)	134 (84.8)	348 (82.9)	543 (87.7)	0.11
Number of full-term pregnancies[a,c]	2.1 (0.9)	2.4 (1.0)	2.3 (1.0)	2.4 (1.1)	<0.001	2.1 (0.8)	2.4 (1.1)	2.3 (1.1)	2.5 (1.1)	<0.001	2.1 (0.8)	2.4 (1.1)	2.4 (1.1)	2.4 (1.1)	<0.001
Age at 1st full-term pregnancy (y)[a,c]	25.5 (4.0)	25.2 (4.4)	25.7 (4.5)	24.7 (3.9)	<0.001	25.4 (3.9)	25.4 (4.5)	25.4 (4.4)	25.0 (3.9)	0.37	25.4 (4.0)	25.3 (4.3)	25.3 (4.3)	25.0 (4.0)	0.58
Educational level[b]					<0.001					<0.001					<0.001
Primary/no schooling	95 (33.1)	102 (60.7)	98 (26.2)	407 (55.8)		95 (34.7)	97 (59.5)	110 (31.7)	369 (56.0)		99 (35.1)	93 (60.0)	139 (34.6)	340 (56.3)	
Technical/professional/secondary	132 (46.0)	43 (25.6)	167 (44.7)	245 (33.6)		115 (42.0)	47 (28.8)	135 (38.9)	219 (33.2)		118 (41.8)	44 (28.4)	165 (41.0)	189 (31.3)	
Longer education	60 (20.9)	23 (13.7)	109 (29.1)	78 (10.7)		64 (23.4)	19 (11.7)	102 (29.4)	71 (10.8)		65 (23.0)	18 (11.6)	98 (24.4)	75 (12.4)	
Physical activity[b]					<0.001					<0.001					<0.001
Inactive	58 (19.3)	59 (33.7)	68 (17.3)	251 (32.8)		55 (19.0)	62 (37.1)	76 (20.3)	239 (34.8)		57 (19.1)	60 (37.7)	99 (22.9)	216 (34.3)	
Moderately inactive	110 (36.7)	64 (36.6)	134 (34.0)	266 (34.8)		113 (39.0)	59 (35.3)	134 (35.8)	243 (35.4)		113 (37.9)	59 (37.1)	150 (34.7)	227 (36.1)	
Moderately active	73 (24.3)	32 (18.3)	118 (29.9)	145 (19.0)		69 (23.8)	23 (13.8)	84 (22.5)	117 (17.0)		67 (22.5)	25 (15.7)	95 (22.0)	106 (16.9)	
Active	55 (18.3)	18 (10.3)	64 (16.2)	84 (11.0)		48 (16.6)	23 (13.8)	68 (18.2)	76 (11.1)		56 (18.8)	15 (9.4)	78 (18.1)	66 (10.5)	
Missing	4 (1.3)	2 (1.1)	10 (2.5)	19 (2.5)		5 (1.7)	0 (0.0)	12 (3.2)	12 (1.7)		5 (1.7)	0 (0.0)	10 (2.3)	14 (2.2)	
Smoking status[b]					<0.001					<0.001					<0.001
Never	196 (65.3)	105 (60.0)	202 (51.3)	508 (66.4)		187 (64.5)	107 (64.1)	182 (48.7)	481 (70.0)		194 (65.1)	100 (62.9)	241 (55.8)	422 (67.1)	
Former smoker	50 (16.7)	36 (20.6)	109 (27.7)	145 (19.0)		49 (16.9)	34 (20.4)	119 (31.8)	114 (16.6)		55 (18.5)	28 (17.6)	122 (28.2)	111 (17.6)	
Current smoker	50 (16.7)	28 (16.0)	72 (18.3)	96 (12.5)		49 (16.9)	25 (15.0)	63 (16.8)	85 (12.4)		43 (14.4)	31 (19.5)	60 (13.9)	88 (14.0)	
Unknown	4 (1.3)	6 (3.4)	11 (2.8)	16 (2.1)		5 (1.7)	1 (0.6)	10 (2.7)	7 (1.0)		6 (2.0)	0 (0.0)	9 (2.1)	8 (1.3)	
Diabetes[b]					<0.001					<0.001					<0.001
Yes	5 (1.9)	5 (3.1)	5 (1.5)	41 (6.2)		5 (2.0)	5 (3.3)	3 (1.0)	42 (7.0)		4 (1.5)	6 (4.1)	4 (1.1)	41 (7.3)	
Alcohol intake (g/d)[a,i]	8.0 (11.3)	7.1 (10.4)	8.6 (11.2)	5.6 (8.9)	<0.001	8.1 (11.4)	7.7 (10.6)	8.7 (10.8)	6.0 (9.7)	<0.001	7.5 (10.5)	8.8 (12.1)	7.5 (10.5)	6.6 (9.9)	0.10
Total energy intake (kcal/d)[a]	2,023.2 (566.6)	1,965.9 (519.5)	1,892.0 (535.1)	1,866.2 (577.7)	<0.001	2,044.8 (555.4)	1,963.9 (532.9)	1,917.7 (527.7)	1,897.0 (590.6)	0.002	2,039.0 (554.2)	1,970.7 (535.4)	1,888.7 (500.2)	1,915.1 (611.9)	0.002
C-peptide (ng/mL)[a,h]	0.9 (0.3)	1.0 (0.3)	2.2 (1.2)	2.6 (1.4)	<0.001	0.9 (0.3)	1.0 (0.3)	2.1 (1.0)	2.6 (1.5)	<0.001	0.9 (0.3)	1.0 (0.3)	2.2 (1.1)	2.6 (1.5)	<0.001
Height (cm)[a]	161.8 (6.8)	159.1 (7.0)	163.5 (6.4)	159.5 (6.7)	<0.001	160.9 (7.2)	160.1 (6.5)	161.9 (6.5)	159.5 (6.7)	<0.001	161.5 (6.9)	158.9 (6.6)	161.7 (6.5)	159.4 (6.7)	<0.001
Body mass index (kg/m^2)[a]	22.3 (1.7)	27.9 (2.7)	22.8 (1.5)	30.1 (4.4)	<0.001	22.6 (2.1)	27.4 (3.2)	23.7 (2.3)	30.1 (4.7)	<0.001	23.6 (3.0)	25.9 (3.6)	25.5 (4.1)	29.5 (5.0)	<0.001
Waist circumference (cm)[a]	73.0 (5.5)	85.4 (7.5)	75.4 (6.0)	90.7 (10.8)	<0.001	72.2 (4.5)	86.7 (6.2)	74.1 (4.4)	92.2 (9.7)	<0.001	73.8 (6.4)	84.4 (8.3)	77.2 (7.7)	91.7 (10.6)	<0.0001
Waist/hip ratio (cm/cm)[a]	0.76 (0.06)	0.81 (0.07)	0.78 (0.06)	0.83 (0.07)	<0.001	0.75 (0.05)	0.83 (0.07)	0.76 (0.05)	0.84 (0.06)	<0.001	0.74 (0.03)	0.85 (0.06)	0.75 (0.03)	0.86 (0.05)	<0.0001

[a]Mean (SD).
[b]*N* (%).
[c]Among parous women. NW, normal weight; OW/OB, overweight and obesity.
[d]Metabolically healthy/normal weight (BMI < 25 kg/m^2 or Waist circumference <80 cm or Waist-to-hip ratio <0.8) plus below tertile 1 of C-peptide.
[e]Metabolically healthy/overweight (BMI ≥ 25 kg/m^2, or Waist circumference ≥80 cm or Waist-to-hip ratio ≥0.8), plus below tertile 1 of C-peptide.
[f]Metabolically unhealthy/normal weight (BMI < 25 kg/m^2 or Waist circumference <80 cm or Waist-to-hip ratio <0.8), plus above tertile 1 of C-peptide.
[g]Metabolically unhealthy/overweight (BMI ≥ 25 kg/m^2, or Waist circumference ≥80 cm or Waist-to-hip ratio ≥0.8), plus above tertile 1 of C-peptide.
[h]Median (Interquartile range) among controls: 1.57 (1.05–2.32) and cases: 1.75 (1.16–2.64).
[i]Median (Interquartile range) among controls: 2.5 (0.3–10.8) and cases: 2.1 (0.2–9.3).

education, higher alcohol intake, and greater prevalence of current smoking and was less frequently classified as physically active. In contrast with this, control participants in the MU/OW group (considering the BMI classification) were less likely to be current smokers and to have longer education, reported lower alcoholic intake and were more frequently classified as physically active than MH/OW. It is important to note that around 40% of the controls were classified in the MU/OW group whereas only around 11% were classified in the MH/OW group. The results based on WC and WHR were broadly similar to those based on BMI.

The results for the associations between metabolically defined body size phenotypes and endometrial cancer risk when adjusted for potential cofounders are described below by the phenotype categories (**Table 3**).

MH/OW

When using BMI and WHR cutoff points, participants classified as MH/OW were at a higher risk of endometrial cancer compared with MH/NW participants, albeit the associations were not statistically significant (OR_{BMI}, 1.40; 95% CI, 0.91–2.15 and OR_{WHR}, 1.17; 95% CI, 0.75–1.81) and were at a statistically significant lower risk of endometrial cancer than their MU/OW counterparts (OR_{BMI}, 0.44; 95% CI, 0.26–0.74 and OR_{WHR}, 0.43; 95% CI, 0.25–0.76). In contrast, when using WC cutoff points, MH/OW women were at statistically significant higher risk of endometrial cancer compared with MH/NW participants (OR, 1.94; 95% CI, 1.24–3.04) and they were at lower risk of endometrial cancer compared with the MU/OW (OR, 0.80; 95% CI, 0.49–1.31), although the association was not statistically significant.

MU/NW

MU/NW were at statistically significant higher risk of endometrial cancer than their MH/NW counterparts when using WC (OR, 1.48; 95% CI, 1.05–2.10) and WHR (OR, 1.68; 95% CI, 1.21–2.35) cutoff points, whereas the results for the BMI cutoff points were non-significant (OR, 1.16; 95% CI, 0.82–1.64).

MU/OW

MU/OW participants were at statistically significantly higher risk of endometrial cancer compared with MH/NW participants considering BMI (OR, 2.38, 95% CI, 1.73–3.27), WC (OR, 2.69; 95% CI, 1.92–3.77), and WHR (OR, 1.83; 95% CI, 1.32–2.54) cutoff points.

Sensitivity analyses

Similar results were observed when excluding cases diagnosed within the first 2 years of follow-up, excluding individuals with diabetes, as well as when the analyses were restricted to individuals with type 1 endometrial cancer or restricted to phase 2 samples (Supplementary Table S5). The results restricted to non-exogenous hormone users and to fasting subjects were also broadly similar; however, most of the results were not statistically significant due to the reduced sample size (Supplementary Table S5). Exclusion of premenopausal participants did not lead to substantial changes in the study results for BMI cutoff points, but a few changes were observed for WC and WHR cutoff points (Supplementary Table S5). Sensitivity analyses also showed similar results when using C-peptide quartiles and median cutoff points to define the metabolic health body size phenotypes (Supplementary Table S6). In addition, results defining the

Table 3. Risk of endometrial cancer incidence associated with metabolic health-defined body size phenotypes using anthropometric and C-peptide tertile cutoff points in the EPIC.

	Metabolically healthy		Metabolically unhealthy		
Body size definition	**Normal weight[a]**	**Overweight/obesity[b]**	**Normal weight[c]**	**Overweight/obesity[d]**	***P***
BMI					
N cases/controls	121/179	81/94	166/228	449/316	
Basic model	1.00	1.34 (0.90–1.99)	1.06 (0.77–1.47)	**2.29 (1.71–3.07)**	<0.0001
		0.45 (0.28–0.72)		1.00	0.0008
Adjusted model	1.00	1.40 (0.91–2.15)	1.16 (0.82–1.64)	**2.38 (1.73–3.27)**	<0.0001
		0.44 (0.26–0.74)		1.00	0.0022
WC					
N cases/controls	110/180	83/84	169/205	397/290	
Basic model	1.00	**1.86 (1.23–2.81)**	**1.41 (1.02–1.95)**	**2.58 (1.89–3.53)**	<0.0001
		0.69 (0.44–1.07)		1.00	0.0975
Adjusted model	1.00	**1.94 (1.24–3.04)**	**1.48 (1.05–2.10)**	**2.69 (1.92–3.77)**	<0.0001
		0.80 (0.49–1.31)		1.00	0.3821
WHR					
N cases/controls	125/173	68/91	225/207	341/288	
Basic model	1.00	1.06 (0.71–1.60)	**1.55 (1.14–2.11)**	**1.76 (1.30–2.39)**	<0.0001
		0.46 (0.28–0.76)		1.00	0.0025
Adjusted model	1.00	1.17 (0.75–1.81)	**1.68 (1.21–2.35)**	**1.83 (1.32–2.54)**	<0.0001
		0.43 (0.25–0.76)		1.00	0.0033

Note: In bold, we highlight the results that were statistically significant. Sub-sample analyses are also presented in this table. Values are OR (95% CI). BMI, Body Mass Index; WC, waist circumference, WHR, Waist-to-Hip ratio. Basic model was conditioned on matching factors only. Adjusted model was conditioned on matching factors, with additional adjustment for age at menopause, age at menarche, parity, hormone use, physical activity index, smoking status, educational level, alcohol intake, height, energy intake and diabetes; P_{trend}.

[a]Metabolically healthy/normal weight (BMI < 25 kg/m^2 or waist circumference <80 cm or waist-to-hip ratio <0.8) plus below tertile 1 of C-peptide.

[b]Metabolically healthy/overweight (BMI ≥ 25 kg/m^2, or waist circumference ≥80 cm or waist-to-hip ratio ≥0.8), plus below tertile 1 of C-peptide.

[c]Metabolically unhealthy/normal weight (BMI < 25 kg/m^2 or waist circumference <80 cm or waist-to-hip ratio <0.8), plus above tertile 1 of C-peptide.

[d]Metabolically unhealthy/overweight (BMI ≥ 25 kg/m^2, or waist circumference ≥80 cm or waist-to-hip ratio ≥0.8), plus above tertile 1 of C-peptide.

upper tertile as the MU group mirrored the main findings (Supplementary Table S7).

Discussion

In this prospective analysis of metabolic health and endometrial cancer risk, MU/NW and MU/OW participants, defined by C-peptide levels, were at higher endometrial cancer risk compared with MH/NW women. In addition, MH/OW women were at higher endometrial cancer risk compared with MH/NW women. These results indicate that women with higher levels of insulin are at elevated risk of endometrial cancer regardless of their body size; however, being OW raises endometrial cancer risk regardless of insulin profile.

Many, but not all, prior studies have shown a similar pattern of results for the relationships of metabolically defined body size phenotypes with cardiovascular disease, type 2 diabetes, all-cause mortality, open-angle glaucoma and obesity-related cancers (17–26, 28, 37, 38). Our results lend further support to the notion that, even though higher body size metrics are associated with increased endometrial cancer risk, the assessment of metabolic dysfunction regardless of body size may be an additional tool for risk stratification. Importantly, the study showed that NW women with metabolic dysfunction have elevated risk for endometrial cancer. The potential mechanisms underlying this relationship may involve the direct effect of insulin on normal endometrial and malignant cells, as the insulin receptor is commonly expressed in the tumor cells (39). However, multiple other factors may occur downstream of insulin signaling to impact endometrial tumorigenesis, such as chronic inflammation and sex hormone disruption (10, 15, 16, 40).

The factors influencing the development of metabolic dysfunction have been investigated and several hypotheses have been proposed, including differences in body fat distribution, poor diet and physical inactivity, and chronic inflammation (21, 41–43). It has been suggested that individuals with metabolic dysfunction tend to have higher intakes of sugar, sugar-sweetened beverages, and saturated fat as well as lower intakes of fruits, whole grains, and protein from vegetable sources compared with MH individuals (21). On the other hand, MH individuals tend to spend more time in moderate to vigorous physical activities and less time in sedentary activities compared with MU individuals (41, 44). Adipose tissue biology and function, including the genetic determinants of body fat distribution, depot-specific fat metabolism, adipose tissue plasticity and, particularly, adipogenesis also play a role (42). However, more research is needed to better understand the mechanisms underlying the development of metabolic dysfunction, including the potential role of the gut microbiota (42).

In the current analysis, individuals with OW or obesity, regardless of their metabolic health status, were at elevated endometrial cancer risk compared with MH/NW individuals. This is in line with previous results from the EPIC cohort showing that obesity (including higher WC and WHR) was associated with higher endometrial cancer risk compared with NW individuals (4). The results for the WC-specific cutoff point were stronger and more consistent compared with the other anthropometric cutoff points. These findings suggest that greater abdominal fat accumulation may impact endometrial cancer risk irrespective of insulin levels. A potential pathway underlying this relationship may include higher levels of estrogen that are synthesized with greater abdominal fat in both premenopausal (45) and postmenopausal women (46), given that higher exposure to unopposed estrogen is an established risk factor for endometrial cancer (47–50). Adipocyte hypertrophy– and hyperplasia-stimulated pro-inflammatory immune response, chronic fibrosis, and vascular inflammation are also potential mechanisms that create a microenvironment conducive to carcinogenesis (47, 51).

To our knowledge, this is the first investigation of metabolically defined body size phenotypes based on C-peptide levels and endometrial cancer risk in a prospective cohort setting. The long-term follow-up and high number of incident endometrial cancer cases recorded is a major strength of this study. However, some limitations of the current study should also be considered. First, although there is no universal definition of "metabolic health," the analysis used only C-peptide levels as a marker of metabolic health whereas there are more than 30 other possible definitions that have been used in different studies, including homeostatic model assessment of insulin resistance (HOMA-IR; using insulin and glucose measures; refs. 21, 43). C-peptide may be a better indicator for long-term insulin secretion than measuring insulin levels owing to its longer half-life (52). In the current study, hyperinsulinemia was defined on the basis of tertiles of C-peptide level in controls, which was supported by the results for the association between C-peptide tertiles and endometrial cancer risk showing elevated risk for the upper two tertiles. This methodology has also been used in previous EPIC studies classifying individuals according to their metabolically defined body sized phenotypes (17). Furthermore, analyses that used quartiles and median of C-peptide levels showed a similar pattern of results. However, future studies should aim to define clinically relevant cutoff points for normal C-peptide levels, which can potentially be used for stratification for endometrial cancer risk. Finally, results from the current study are largely applicable to white European women and future studies should investigate other populations, such as black women who tend to have worse prognosis from endometrial cancer (53, 54).

In conclusion, we have shown that women with metabolic dysfunction appear to have higher risk of endometrial cancer regardless of their body size. Therefore, it is possible that using only anthropometric measurements to identify women at higher risk of endometrial cancer would exclude normal-weight individuals with poor metabolic health and could underestimate the risk among OW individuals with hyperinsulinemia. MU/NW women represented 20% to 30% of the current sample; therefore, this proportion of women would be missed when using only body size for identifying women at higher risk of endometrial cancer. Thus, classifying populations by metabolically defined body size phenotypes may be of greater utility in identifying individuals at higher risk for endometrial cancer who would not have otherwise been identified solely by anthropometric measures. Our findings also showed that OW status may raise endometrial cancer risk even among women with lower insulin levels, suggesting that obesity-related pathways are important for this cancer beyond insulin. The combination of anthropometric measures with metabolic parameters, such as C-peptide, may allow more precise identification of the strata of the population at greater endometrial cancer risk, which could be targeted for prevention strategies.

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Authors' Contributions

N. Kliemann: Conceptualization, writing–original draft, writing–review and editing. **R. Ould Ammar:** Conceptualization, writing–review and editing. **C. Biessy:** Conceptualization, formal analysis, writing–review and editing. **A. Gicquiau:** Data curation, validation, writing–review and editing. **V. Katzke:**

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