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ORIGINAL PAPER

Metabolic syndrome and risk of endometrial cancer in postmenopausal women: a prospective study

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Abstract

Background Obesity is a strong risk factor for endometrial cancer, but it is unclear whether metabolic syndrome (MetS) contributes to endometrial cancer risk over and above the contribution of obesity.

Methods We examined the association of MetS and its components with risk of endometrial cancer in a sub-cohort of 24,210 women enrolled in the Women's Health Initiative cohort study. Two variants of the National Cholesterol Education Program Adult Treatment Panel III definition of the MetS were used: one including and one excluding waist circumference (WC). Cox proportional hazards models were used to estimate the association of the study exposures with disease risk.

Results When WC was included in the definition, MetS showed an approximately two-fold increase in endometrial cancer risk (HR 2.20; 95% CI 1.61–3.02); however, when WC was excluded, MetS was no longer associated with risk. We also observed that women with hyperglycemia, dyslipidemia and hypertension, in combination, had almost a twofold increased risk of endometrial cancer, independent of WC (HR 1.94; 95% CI 1.09, 3.46). Glucose, and, in particular, WC and body mass index were also positively associated with risk.

Conclusions Our findings suggest that MetS may predict risk of endometrial cancer independent of obesity among women with the remaining four Mets components.

Keywords Metabolic syndrome · Obesity · Abdominal adiposity · Endometrial cancer · Postmenopausal women

Introduction

Metabolic syndrome (MetS) is a constellation of risk factors including obesity, hypertension, insulin resistance, and dyslipidemia [1]. The prevalence of MetS in the United States is currently estimated at 34.2% [2]. Its role as a predictor of chronic diseases remains debatable. However, epidemiological evidence suggests that it is a risk factor for major chronic diseases including cardiovascular diseases (CVDs) and diabetes [3, 4]. Some studies have also associated MetS with certain cancers. Few studies have also examined the association of MetS and its components with risk of endometrial cancer [5–11], and only two of these have been cohort studies [5, 6]. All found a positive association between MetS and risk of endometrial cancer, with risk estimates ranging from 1.37 [5] to 2.77 [8]. Among the MetS components, studies found that waist circumference (WC), hyperglycemia, hypertriglyceridemia and hypertension were positively associated with risk of endometrial cancer [5, 9], but, in most studies, WC, a measure of obesity, has had the strongest association with risk [5, 9, 11].

Whether MetS contributes to risk of endometrial cancer beyond the contribution of obesity is unclear. To address this issue, in a case–control study, Rosato et al. conducted sensitivity analyses whereby measures of adiposity (body mass index (BMI) and WC) were excluded from the MetS variable, and, a statistically positive significant association was evident [8]. Further, in analyses stratified by BMI category, a prospective cohort study by Bjørge et al. observed a positive

Rhonda Arthur and Geoffrey C. Kabat have equal contribution.

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association between MetS and risk of endometrial cancer, particularly among women in the highest BMI category [6]. Together, these findings suggest that MetS predicst risk of endometrial cancer beyond the contribution of obesity.

Given the strong association of obesity with risk of endometrial cancer, further prospective studies are needed to further clarify whether MetS predicts risk of endometrial cancer independently of obesity. Hence, in this study, we examined the association between MetS (with and without the inclusion of WC in the definition) and risk of endometrial cancer in a sub-group of 24,210 women within the Women's Health Initiative who had information on anthropometric characteristics, serum lipids, glucose, and blood pressure measured at baseline, and for whom information on a wide range of potential confounding variables was available. We also assessed the associations of the individual MetS components with risk of endometrial cancer.

Materials and methods

The Women's Health Initiative (WHI) is a large, multicenter cohort study designed to advance understanding of the determinants of major chronic diseases among postmenopausal women. It consists of clinical trial (CT, $n = 68{,}132$) and observational study (OS, $n = 93{,}676$) components [12]. The CT component included four randomized controlled intervention studies: hormone therapy (two trials), low-fat dietary modification, and calcium + vitamin D supplementation. Women between the ages of 50 and 79 and representing the major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the US between 1993 and 1998. Details of the study design and reliability of the baseline measures have been published [12, 13]. The study was approved by the institutional review boards of all participating institutions, and all participants provided written informed consent.

At study entry, self-administered questionnaires were used to collect information on demographics; medical, reproductive, and family history; and lifestyle factors, including smoking history, alcohol consumption, dietary habits, and recreational physical activity. Weight and height were measured by trained staff at baseline. Weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. Waist circumference was measured with a tape measure at the narrowest part of the torso between the participant's ribs and iliac crest. BMI was computed as weight in kilograms divided by the square of height in meters. Two blood pressure measurements were obtained ≥ 30 minutes apart, and the average of the 2 measurements was used in the analysis. Questions about physical activity at baseline referred to a woman's usual pattern of activity, including walking and recreational physical activity. "Total leisure-time physical activity" (MET-h/week) was computed by multiplying the number of hours per week of leisure-time physical activity by the metabolic equivalent (MET) value of the activity and summing across all types of activities [14].

Follow-up and ascertainment of outcomes

Clinical outcomes (including new cancer diagnoses) were updated semiannually in the CT and annually in the OS using in-person, mailed, or telephone questionnaires. Self-reports of malignancy were verified by central review of medical records and pathology reports by trained physician adjudicators [15].

The CVD biomarkers subsample

Individuals who had measurements of fasting baseline serum glucose, lipids, and other clinical parameters in sub-studies within WHI were assembled into the CVD Biomarkers Subsample ($n = 24{,}210$). Some sub-studies entailed selecting a random sample; others involved selection of participants based on specific age and race/ethnicity criteria within the hormone therapy trials; and another sub-study was a nested case–control study within the hormone therapy trials with random sampling of controls.

Assays for glucose, HDL-C and triglycerides

Blood was obtained after at least 8 h of fasting for 99.8% of participants in the subsample. Specimens were centrifuged, and serum and plasma were frozen at − 70 °C and shipped on dry ice to a central processing facility, where they were stored at − 80 °C. HDL-C was measured in serum using the HDL-C Plus 3rd Generation Direct Method (Roche) on the Roche Modular P Chemistry Analyzer. Triglycerides were measured in serum using Triglyceride GB reagent (Roche) on the Roche Modular P Chemistry Analyzer. In the vast majority of women ($n = 22{,}314$, 88%), glucose was measured in serum using the Gluco-quant Glucose/hexokinase reagent (Roche Diagnostics, Indianapolis) on the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation); in the remainder, serum glucose was determined by the hexokinase method on the Hitachi 747 (Boehringer Mannheim Diagnostics, Indianapolis, IN). Insulin was determined using the Sandwich Immunoassay (Roche Diagnostics) on Roche Elecsys 2010 Analyzer.

Definition of the metabolic syndrome

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition of MetS was used, defined as meeting ≥ 3 of the 5 following criteria: WC ≥ 88 cm, triglycerides ≥ 150 mg/dl, HDL-C < 50 mg/

dl, glucose ≥ 100 mg/dl and systolic/diastolic blood pressure (BP) ≥ 130/85 mmHg or treatment for hypertension [1]. To assess the relative contribution of WC to the association of the MetS with endometrial cancer, a modified definition that excluded WC from the ATP III definition was used (i.e., presence of the MetS was defined as having ≥ 2 of the 4 remaining components).

Exclusions

Baseline measurements of fasting blood analytes were available for 24,210 women in the sub-sample. We excluded 11,098 women who had a hysterectomy at baseline (including women from the estrogen alone trial), 9 women with a previous history of endometrial cancer, 36 women with incomplete information on the metabolic syndrome components and 6 women with missing information on follow-up time. After exclusions, 13,061 women were available for analysis, among whom, as of February 28, 2017, 176 incident endometrial cancer cases had been diagnosed.

Statistical analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for the association of MetS and its components with risk of endometrial cancer. The outcome was time to diagnosis of endometrial cancer. Cases contributed person-time to the study from their date of enrollment until the date of diagnosis, and non-cases contributed person-time from their date of enrollment until the end of follow-up, date of death, or date of withdrawal from the study, whichever came first. BMI was categorized according to a modification of the World Health Organization classification [18.5–<25.0, 25.0–<30.0, 30.0–<35.0 (Class I obesity), ≥ 35.0 kg/m^2 (Class II and III obesity)]. For our main analyses, the MetS components were classified in accordance with the NCEP ATP III definition: WC: < 88 cm, ≥ 88 cm; glucose: < 100 mg/dL, ≥ 100 mg/dL; HDL-C: ≥ 50 mg/dL, < 50 mg/dL; triglycerides: <150 mg/dL, ≥ 150 mg/dL and high blood pressure: No (< 130/85 mmHg); Yes (≥ 130/85 mmHg or treatment for hypertension). Covariates were selected for inclusion in the final model if associated with risk of endometrial cancer in the literature or if their inclusion altered the parameter estimate by > 10%. All models were adjusted for age (continuous), pack-years of smoking (continuous), alcohol intake (g/d—continuous), physical activity (MET-h/week—continuous), history of diabetes (no, yes), oral contraceptive use (never, ever), hormone therapy use (never, ever), age at menopause (< 45, 45–54, ≥ 55, missing), educational level (less than high school, high school graduate/some college, college graduate, post-college), ethnicity (white, black, other), family history of endometrial cancer (yes, no) and participation in the Observational Study or intervention/placebo/control arm of each clinical trial separately. Since hyperglycemia, dyslipidemia and high blood pressure are associated with obesity, we examined its influence on the associations of these variables with risk of endometrial cancer by additionally adjusting for WC. In the final model, we mutually adjusted for the individual MetS component. Sensitivity analysis using the IDF MetS criteria (defined as having WC > 80 cm plus any two of the following four factors: (1) triglycerides: ≥ 150 mg/dL; (2) HDL: < 50 mg/dL; (3) systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment for hypertension; (4) glucose: (fasting plasma glucose) ≥ 100 mg/dL, or previously diagnosed type 2 diabetes was also performed.

We repeated the main analyses after excluding women with a history of diabetes. We also examined the association with MetS among cases with Type I endometrial cancer (endometrioid carcinoma, adenocarcinoma NOS, and adenocarcinoma with squamous differentiation [16] *n* cases = 143). There were too few cases to examine the association of MetS with risk of Type 2 endometrial cancer. In further analyses, the association of MetS with endometrial cancer was stratified by variables which have been shown to influence risk of endometrial cancer, including smoking status, hormone therapy, and BMI. P for interaction was estimated by including interaction terms in Cox regression models and testing their coefficients by the using Wald tests. A test for linear trend over categories of BMI was performed by assigning the median value to each category and modeling this variable as a continuous variable.

To assess whether addition of triglycerides, HDL cholesterol, blood pressure, and glucose improved the predictive accuracy of WC, C-statistics were used (equivalent to the area under the receiver operating curve (AUROC)) for multivariable Cox proportional hazard regression models with WC alone, and WC plus the other MetS components (triglycerides, HDL cholesterol, blood pressure, and glucose). A similar analysis was conducted to assess whether WC improved the predictive discrimination of BMI.

All *P*-values are 2-sided. All analyses were performed using Stata 14.1 (StataCorp, College Station, TX, USA).

Results

Compared with non-cases, endometrial cancer cases had higher mean baseline BMI, WC, serum glucose and lower mean HDL-C and pack-years of smoking and earlier age of menarche (Table 1). Cases not included in the CVD subsample had lower mean baseline BMI, WC, systolic blood pressure, but higher alcohol intake and physical activity level, than those included in the CVD sub-sample. They were also

Table 1 Distribution of baseline characteristics among endometrial cancer cases and non-cases, Women's Health Initiative ($n = 13,061$)

Baseline characteristics	Cases ($n = 176$)	Non-cases ($n = 12,885$)	p-value
Means + SD			
Age	63.4 ± 6.9	64.3 ± 7.2	0.08
Body mass index (kg/m^2)	33.1 ± 7.9	29.1 ± 6.9	< 0.01
Waist circumference (cm)	97.6 ± 16.2	88.6 ± 13.7	< 0.01
Serum glucose	110.9 ± 44.6	102.0 ± 33.1	0.01
Serum HDL-C	51.0 ± 12.5	54.1 ± 13.2	< 0.01
Serum triglycerides	139.1 ± 75.8	132.6 ± 76.8	0.27
Systolic blood pressure	131.3 ± 15.4	129.4 ± 17.8	0.16
Diastolic blood pressure	77.2 ± 8.8	75.8 ± 9.3	0.04
Alcohol intake (g/d)	4.5 ± 11.2	6.4 ± 45.1	0.57
Physical activity (MET-h/week)	9.9 ± 13.7	10.7 ± 13.3	0.43
Pack-years of smoking	7.1 ± 14.4	9.3 ± 18.0	0.09
Proportions (%)			
Education (postgraduate)	29.7	25.4	0.20
Race/ethnicity (white)	52.8	53.2	0.92
Family history of endometrial cancer (yes)	6.3	5.1	0.45
History of diabetes (yes)	10.2	8.2	0.56
Age at menarche (≤ 11 year)	23.9	21.2	0.04
Parity (nulliparous)	10.8	10.6	0.31
Age at menopause (< 45 year)	5.7	10.7	0.17
Oral contraceptive use (yes)	36.9	37.3	0.93
Hormone therapy use (yes)	29.6	27.2	0.49

WC waist circumference, *HDL-C* high density lipoprotein-cholesterol

less likely to report a history of diabetes, but, were more likely to be nulliparous or be HT users (Table S1).

The MetS definitions (including WC) were associated with an approximately twofold increased risk of endometrial cancer (HR 2.27; 95% CI 1.67–3.09 and 2.05; 1.51–2.79; for NCEP and IDF, respectively) (Tables 2 and S2). After excluding WC from the definition, the associations remained positive, but were no longer statistically significant (HR 1.34; 95% CI 0.97–1.84) (Table 1).

The exclusion of women with a history of diabetes did not change the findings for MetS. When the association was restricted to cases with Type I endometrial cancer, the HRs for presence of MetS based on the NCEP criteria was 2.49 (95% CI 1.77–3.50). The corresponding HR for MetS based on the IDF criteria was 2.22 (95% CI 1.55–3.12).

Among the individual MetS components, the multivariate analyses (model 1) demonstrated that relatively large WC, hyperglycemia, low HDL and high blood pressure were associated with increased risk of endometrial cancer (Table 2). However, after additional adjustment for WC, the HRs for HDL and high blood pressure were attenuated and became statistically non-significant (model 2). Waist circumference and hyperglycemia were independently associated with risk of endometrial cancer, even after mutual adjustment for the MetS components, although the HRs were attenuated (model 3). BMI also showed a statistically significant positive association with endometrial cancer (p for trend < 0.001) (Table 2). Overweight women were not at increased risk, whereas the HR for Class I obesity (BMI = 30–<35 kg/m^2) was 2.23 (95% CI 1.34–3.70), and that for Class II obesity (BMI ≥ 35.0 kg/m^2) was 4.16 (95% CI 2.47–7.00) (Table 2).

In analyses according to number of MetS components, we observed a trend towards an increased risk of endometrial with increasing number of MetS components (Table 3). Notably, using the modified NCEP/IDF definitions (i.e. without WC), we observed that those with a combination of hyperglycemia (glucose ≥ 100 mg/dl or history of diabetes), dyslipidemia (triglycerides: ≥ 150 mg/dL or HDL: < 50 mg/dL) and high blood pressure (systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment for hypertension) had increased risk of endometrial cancer (HR 1.94; 95% CI 1.09–3.46) (Table 3).

In stratified analyses, there was a borderline statistically significant heterogeneity in the association by smoking status (the association was stronger among ever smokers compared to never smokers) (Table 3). Differences by age, hormone therapy, and BMI were not statistically significant; however, the numbers in some strata were small (Table 4).

The results of the C-statistics demonstrated that the model with WC plus the remaining components (C: 0.696 95% CI

Table 2 Association of metabolic factors with endometrial cancer, Women's Health Initiative

Variable	Cases *N*	Non-cases *N*	Model 1[a]	95% CI	Model 2[b]	95% CI	Model 3[c]	95% CI
Metabolic syndrome (including WC)								
No	77	7,958	1.00	Ref.	–	–	–	–
Yes	99	4,927	2.27	1.67–3.09	–	–	–	–
Metabolic syndrome (excluding WC)[b]					–	–	–	–
No	69	6,546	1.00	Ref.	–	–	–	–
Yes	107	6,339	1.34	0.97–1.84	–	–	–	–
Body mass index (kg/m^2)								
18.5–< 25.0	25	3,386	1.00	Ref.	–	–	1.00	–
25.0–< 30.0	32	4,552	0.98	0.57–1.64	–	–	0.89	0.52–1.51
30.0–< 35.0	53	2,914	2.59	1.59–4.22	–	–	2.23	1.34–3.70
≥ 35	63	1,872	5.08	3.11–8.32	–	–	4.16	2.47–7.00
P for linear trend			*< 0.001*		–	–	–	*< 0.001*
WC (cm)								
< 88	49	6,678	1.00	Ref.	–	–	1.00	Ref.
≥ 88	127	6,207	2.91	2.07–4.09	–	–	2.48	1.73–3.56
Glucose (mg/dL)								
< 100	96	8,693	1.00	Ref.	1.00	Ref.	1.00	Ref.
≥ 100	80	4,192	1.99	1.36–2.49	1.45	1.07–1.98	1.41	1.03–1.93
HDL-C (mg/dL)								
≥ 50	86	7,689	1.00	Ref.	1.00	Ref.	1.00	Ref.
< 50	90	5,196	1.65	1.22–2.23	1.32	0.97–1.80	1.30	0.93–1.81
Triglycerides (mg/dL)								
< 150	117	9,078	1.00	Ref.	1.00	Ref.	1.00	Ref.
≥ 150	59	3,807	1.34	0.97–1.85	1.09	0.78–1.52	0.93	0.65–1.32
High blood pressure								
No	62	5,428	1.00	Ref.	1.00	Ref.	1.00	Ref.
Yes	114	7,457	1.40	1.02–1.93	1.18	0.86–1.63	1.13	0.82–1.57

WC waist circumference, *HDL-C* high density lipoprotein-cholesterol

[a]Model 1: Adjusted for age, pack-years of smoking, alcohol intake, physical activity, hormone therapy ever, oral contraceptive ever, menopausal status, education, ethnicity, family history of endometrial cancer and allocation to the observational study or intervention/placebo/control arm of each clinical trial

[b]Model 2: Adjusted for variables in model 1 plus waist circumference

[c]Model 3: Adjusted for variables in model 1 and mutually adjusted for waist circumference, glucose, triglycerides, HDL, high blood pressure

0.658–0.733) performed slightly better than the model with WC alone (C: 0.668; 95% CI 0.628–0.708). However, the model with BMI plus WC (C: 0.722 95% CI 0.685–0.759) had similar predictive value to the model with BMI alone: (C: 0.723 95% CI 0.685–0.762).

Discussion

Among 13,061 postmenopausal women, the presence of MetS was associated with an approximately twofold increased risk of endometrial cancer. When WC was excluded from the MetS definition, the association of MetS with endometrial cancer remained positive, but was no longer statistically significant. However, women who had hyperglycemia, dyslipidemia and hypertension, in combination, had increased risk of endometrial cancer. Among the individual MetS components, WC and glucose had independent positive associations with risk of endometrial cancer. BMI also showed a monotonic, positive association with risk of endometrial cancer.

In keeping with our findings, studies have consistently shown positive associations of MetS with endometrial cancer [5–11], irrespective of the definition used. Very few studies have examined the association between MetS and risk of endometrial cancer by specific subtypes. As with our results, Bjørge et al. [6] found that when the analysis was restricted to Type I tumors, MetS (defined as the standardized sum of z scores for BMI, blood pressure, glucose, cholesterol, and triglycerides) had a similar association to women who were

Table 3 Association of metabolic factors according to NCEP criteria with endometrial cancer, Women's Health Initiative

Variable	Cases *N*	Non-cases *N*	HR[a]	95% CI
Metabolic syndrome (including WC)				
No. of components				
0	15	1,961	1.00	Ref.
1	27	3,036	1.18	0.62–2.21
2	35	2,961	1.65	0.90–3.04
3	44	2,554	2.51	1.39–4.56
4	34	1,626	3.16	1.70–5.86
5	21	747	4.31	2.99–8.49
P for trend			*< 0.001*	
Metabolic syndrome (excluding WC)[b]				
No. of components				
0	26	2,523	1.00	Ref.
1	43	4,023	0.88	0.54–1.45
2	47	3,310	1.09	0.66–1.80
3	34	2,107	1.16	0.68–1.98
4	26	922	1.94	1.09–3.46
P for trend			*0.017*	

WC waist circumference

[a]Adjusted for age, pack-years of smoking, alcohol intake, physical activity, hormone therapy ever, oral contraceptive ever, menopausal status, education, ethnicity, family history of endometrial cancer and allocation to the observational study or intervention/placebo/control arm of each clinical trial

[b]Also adjusted for WC

Table 4 Association of the metabolic syndrome with endometrial cancer stratified by potential effect modifiers

	Cases/non-cases *N*	HR[a]	95% CI	*P* for heterogeneity
Age (years)				
< 65	92/5,929	2.55	1.66–3.92	0.31
≥ 65	84/6,956	1.92	1.24–2.98	
Smoking				
Never smoker	101/6,663	1.73	1.16–2.59	0.05
Ever smoker	73/6,095	3.45	1.10–5.69	
Missing	2/127			
Hormone therapy use				
Never	124/9,378	2.38	1.62–3.49	0.21
Ever	52/3,507	1.83	1.03–3.25	
Hormone therapy use (excluding women from the HT intervention)				
Never	96/6,188	2.61	1.71–3.99	0.17
Ever	38/2,469	1.72	0.88–3.35	
BMI (kg/m^2)				
18.5–< 25.0	25/3,386	1.83	0.61–5.46	0.20
25.0–< 30.0	32/4,552	1.31	0.62–2.76	
≥ 30.0	116/4,859	1.57	1.04–2.36	
Missing	3/162			

HT hormone therapy, *BMI* body mass index

[a]With the exception of the stratifying variable, models were adjusted for age, pack-years of smoking, alcohol intake, physical activity, hormone therapy use, oral contraceptive use, menopausal status, education, ethnicity, allocation to the observational study or intervention/placebo/control arm of each clinical trial

included in the total case group. Using similar MetS definitions to those in our study, in a very large case–control study using the SEER-Medicare database, [9] showed that MetS was associated with increased odds of Type 1 endometrial cancer, based on the NCEP and IDF definitions (OR 1.41; 95% CI 1.32–1.50 and 2.03; 1.83–2.26, respectively).

Several studies stratified the association of MetS and its components by other factors, including age, smoking status, hormone therapy, and BMI [5–8]. Although a stronger association of MetS or its components with endometrial cancer was observed in participants with higher BMI in two studies [5, 6], tests for heterogeneity were not statistically significant, and there was no heterogeneity in the association across strata of other factors (hormone use, menopausal status, and physical activity). Smoking is believed to lower risk of endometrial cancer through its antiestrogenic effect [17]. However, in the current study, we found evidence to suggest that smoking is an effect modifier for the association between MetS and risk of endometrial cancer, with risk being greater among ever than never smokers. Using a slightly different MetS definition (defined as having diabetes, hypertension, hyperlipidemia, and WC > 88 cm or BMI ≥ 30 kg/m^2 for women with missing information for WC), findings from a case–control study by Rosato et al showed a similar greater risk of endometrial cancer among smokers who had at least three of the metabolic syndrome components compared to never smokers with the corresponding number of components (never-smokers: OR 3.62, 95% CI 1.99–6.57 and ever-smokers: OR 8.65, 2.96–25.27) [8]. These findings suggest that any potential beneficial effect of smoking is offset by the influence of metabolic abnormalities. Further studies are needed to confirm our findings and to elucidate why the risk of endometrial cancer among smokers with Mets may be greater risk than never smokers with MetS.

The utility of MetS in etiologic and mechanistic research is difficult to interpret for several reasons. First, MetS combines heterogeneous clinical factors involved in different mechanistic pathways. Second, the components are dichotomized, resulting in a loss of valuable information. Finally, despite the variations in the magnitude of the associations between the individual MetS components and risk of endometrial cancer, each component is given equal weight. Among the components, measures of adiposity, including, WC and BMI have been shown to have the strongest associations with endometrial cancer risk in most studies [5, 9, 11], and that these associations were independent of other MetS components [5, 9]. Similarly, in the current study, WC and BMI were the strongest predictors of endometrial cancer risk. Moreover, after exclusion of measures of WC from the MetS definition, the association between MetS and endometrial cancer was no longer apparent. Given the strong association between adiposity and endometrial cancer, it is not surprising that, after exclusion of measures of WC from the NCEP/IDF MetS definition, the association between MetS and endometrial cancer was no longer apparent. While this finding suggests that the observed association between MetS and endometrial cancer is largely explained by level of adiposity, our finding of an almost twofold increased risk of endometrial cancer among women with the other MetS components (i.e. hypertriglyceridemia, low HDL, hyperglycemia and high blood pressure) suggest that the association between MetS and endometrial cancer risk is not solely explained by level of adiposity. Although obesity is known to be strongly associated with risk of endometrial cancer, few studies have assessed whether the association of MetS with risk of endometrial cancer is independent of level of adiposity. Evidence to support the view that the association between MetS and risk of endometrial cancer is independent of level of adiposity was provided in a case–control study and a prospective cohort study. Specifically, a case–control by Rosato et al. found a 73% HR 1.73 (95% CI 1.14–2.64) increased risk of endometrial cancer among women with three or more metabolic abnormalities including dyslipidemia (low HDL and high triglyceride levels), hyperglycemia and hypertension [8]. Further, an earlier prospective cohort study, by Tone Bjørge et al. found an association between MetS (excluding BMI) and risk of endometrial cancer, particularly among women in the highest BMI category [6].

In addition to WC and BMI, glucose was the only other MetS component which was found to be independently associated with risk of endometrial cancer after mutual adjustments for the individual MetS components (and other potential confounders). This finding is consistent with those of two previous studies [5, 9]. However, earlier studies observed that other components of MetS were also associated with endometrial cancer after mutual adjustment [5, 7, 9] and that risk increased with increasing number of MetS factors [5, 6, 8, 9]. The lack of association in our study may be due to limited power resulting from the small sample size. It is also probable that the associations of the remaining components with risk of endometrial cancer are mediated by adiposity, as adjusting for WC significantly attenuated their risk estimates.

The strong association of WC with endometrial cancer risk suggests that centrally located adipose tissue may play an important role in endometrial cancer. The association may reflect the effects of visceral (i.e., intra-abdominal) fat, as visceral fat is metabolically more active than subcutaneous abdominal fat and secretes larger amounts of cytokines and hormones compared to subcutaneous fat [18]. The weaker, but also consistent association of glucose with endometrial cancer, which was observed in the entire WHI CVD Biomarkers subsample [19], may reflect several mechanisms. Elevated glucose levels can aggravate

insulin resistance [20], favor the selection of malignant clones [21], and confer a growth advantage on cancer cells [22, 23].

Among the strengths of our study are the prospective cohort design, the availability of measured anthropometric variables, as well as detailed information on potential confounding or modifying factors, including reproductive factors and exogenous hormone use that were not available in some studies [6, 24]. In addition, we carried out sensitivity analyses, excluding women with a history of diabetes and restricting the analysis to Type I endometrial cancer. This is also one of the few prospective studies to examine whether the association between MetS and risk of endometrial cancer is independent of obesity. Limitations include the fact that the non-random selection of women included in some of the sub-studies may have influenced the results. Furthermore, the Women's Health Initiative is a study of postmenopausal women, and, therefore, our results may not apply to younger, premenopausal women. Also, a history of diabetes was based on self-report. Finally, the number of endometrial cancer cases (overall) was relatively small, and therefore, the study may not have been adequately the powered to detect an association between some of the individual MetS components and risk of endometrial cancer. Finally, the number of type Type II endometrial cancer cases was also too small to permit separate analysis, and our assessment of heterogeneity across other factors was also limited by small numbers.

Conclusion

Although the association between MetS and risk of endometrial cancer appears to be largely explained by a woman's level of adiposity, we found evidence to suggest that MetS contributes to risk of endometrial cancer independently of obesity. However, given the limitations of this study, other studies are needed to confirm our findings.

Author contributions Conception and design: TER, GCK, RA; Development of methodology: GCK, TER, RA; Acquisition of data: GCK; Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): GCK, TER, RA, MYK; Writing, review, and/or revision of the manuscript: GCK, TER, RA, MYK, RAW, AHS, JW-W, GYFH, KWR, LHK, JL, JB-D, MSS, HS, SW-S.

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Data availability The datasets used and/or analysed during the current study are available from the Women's Health Initiative Coordinating Center on reasonable request.

Compliance with ethical standards

Conflict of interest No potential conflicts of interest were disclosed.

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