CANCER EPIDEMIOLOGY

Body size, body composition and endometrial cancer risk among postmenopausal women in UK Biobank

Wemimo Omiyale1 | Naomi E. Allen1,2 | Siân Sweetland3

1Clinical Trial Service and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
2UK Biobank Ltd, Stockport, UK
3Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

Correspondence
Wemimo Omiyale, Clinical Trial Service and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK.
Email: wemimo.omiyale@ndph.ox.ac.uk

Abstract
Previous studies on the association of adiposity with endometrial cancer risk have mostly used body mass index (BMI) as the main exposure of interest. Whether more precise measures of body fat, such as body fat percentage and fat mass estimated by bioimpedance analyses, are better indicators of risk than BMI is unknown. The role of central adiposity and fat-free mass in endometrial cancer development remains unclear. We used Cox regression models to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the associations of various measures of body size/composition with the risk of endometrial cancer among 135,110 postmenopausal women enrolled in UK Biobank. During a mean follow up of 6.8 years, 706 endometrial cancers were diagnosed, with a mean age at diagnosis of 65.5 years. The HRs (95% CIs) for endometrial cancer per 1 SD increase in BMI, body fat percentage and fat mass were broadly comparable, being 1.71 (1.61-1.82), 1.92 (1.75-2.11) and 1.73 (1.63-1.85), respectively. There was an indication of positive association between central adiposity, as reflected by waist circumference (HRper 1-SD increase = 1.08, 95% CI: 1.00-1.17) and waist to hip ratio (HRper 1-SD increase = 1.13, 95% CI: 1.01-1.26), and endometrial cancer risk after accounting for BMI. Fat-free mass was not an independent predictor of risk in this cohort. These findings suggest that body fat percentage and fat mass are not better indicators of endometrial cancer risk than BMI. Further studies are needed to establish whether central adiposity contributes to risk beyond overall adiposity.

KEYWORDS
bioimpedance, BMI, body composition, endometrial cancer

1 | INTRODUCTION

Excess adiposity, often defined by body mass index (BMI), is an established risk factor for endometrial cancer.1–8 However, BMI reflects both fat and fat-free mass, which may have different associations with disease risk, and it also does not assess fat distribution, which varies considerably even among individuals with a similar BMI.9

Abbreviations: BMI, body mass index; CI, confidence interval; DEXA, dual-energy X-ray absorptiometry; EPIC, European Prospective Investigation into Cancer and Nutrition; gsCI, group-specific confidence intervals; HR, hazard ratio; HRT, hormone replacement therapy; ICD-10, International Statistical Classification of Diseases and Related Health Problems tenth revision; IGF-1, insulin-like growth factor-1; MRI, magnetic resonance imaging; NHS, National Health Service; RDR, regression dilution ratio.

Received: 20 January 2020 Revised: 7 April 2020 Accepted: 17 April 2020
DOI: 10.1002/ijc.33023

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Int. J. Cancer. 2020;147:2405–2415.
Consequently, BMI may not accurately capture the true relationship between adiposity and endometrial cancer risk. Body fat percentage and fat mass are more precise measures of overall fatness than BMI. Whether these measures are more strongly related to endometrial cancer risk than BMI is unknown.

The distribution of body fat, in particular central adiposity, is linked to several metabolic abnormalities including insulin resistance and inflammation that are associated with endometrial cancer development.\textsuperscript{10,11} Although several studies have evaluated central adiposity, typically assessed by waist circumference, waist to hip ratio or waist to height ratio, in relation to risk of endometrial cancer,\textsuperscript{12-21} it remains unclear whether central adiposity contributes to risk independently of overall adiposity.

Beyond adiposity, other aspects of body size and composition may also influence endometrial carcinogenesis. Height, a marker of early life and nutritional factors, has been associated with increased risk of endometrial cancer in some studies\textsuperscript{22-25} but not others.\textsuperscript{13,19,26-28} Fat-free mass has also been associated with an increased risk of endometrial cancer,\textsuperscript{29} however, it is unclear whether this association reflects confounding by BMI.

We used data from women in UK Biobank to assess the associations of several measures of body size and body composition with the risk of endometrial cancer. Specifically, we investigated whether more precise measures of overall adiposity (body fat percentage and fat mass) are better indicators of endometrial cancer risk than BMI, and whether central adiposity (waist circumference, waist to hip ratio, waist to height ratio, trunk fat percentage) contributes to risk independently of overall adiposity.

### 2 | METHODS

#### 2.1 | Study population

UK Biobank is a prospective study designed to investigate the associations of genetic and environmental factors with the risk of chronic disease. Details of the recruitment, data collection and follow-up are described elsewhere.\textsuperscript{30} Briefly, between 2006 and 2010, about 9.2 million individuals aged 40-69 years who were registered with the National Health Service (NHS) and lived within travelling distance (approximately 25 miles) of 22 assessment centres in England, Wales and Scotland, were invited to participate in the study. Approximately 500 000 individuals joined the study and provided data on a wide range of exposures including demographic, lifestyle, reproductive and medical histories. Physical measures and biological samples were also obtained from participants during the initial assessment. About 4 to 5 years after the baseline visit, a subset of the cohort (\(\approx 200000\) individuals) underwent a repeat assessment of baseline measures to allow for correction of risk estimates for regression dilution bias due to random measurement error of exposures.

The current study included only women (\(n = 273402\)). We excluded 51 213 women with a history of hysterectomy at baseline, 973 women with unknown hysterectomy status, 14 562 women with a previous history of invasive cancer (except nonmelanoma skin cancer), 3832 women with missing data on any of the body size/composition measures of interest, 66 women with extreme values of BMI (\(\text{BMI} < 16\) or \(\geq 60\ \text{kg/m}^2\)) and 10 352 women with unknown menopausal status. Because the biological mechanism through which adiposity influences the risk of endometrial cancer differs between premenopausal and postmenopausal women and because of the relatively small number of premenopausal women in this cohort (\(n = 57294\)), we restricted the analysis to postmenopausal women only (defined as women who self-reported menopause in the baseline questionnaire, or who had a history of bilateral hysterectomy at baseline, or who were aged 55 years or above at baseline; \(n = 135110\)).

#### 2.2 | Assessment of body size and composition

At baseline, trained personnel collected data on body size and composition from all participants using a standard protocol. Height (cm) was measured to the nearest 0.1 cm using a Seca 240 cm height measure, with participants standing barefoot and with their head positioned in the Frankfort plane. Waist and hip circumference (cm) were measured using a Seca 200 cm tape. Waist circumference was measured at the narrowest part of the trunk or the level of the umbilicus at the end of a normal expiration, while hip circumference was measured at the widest part of the buttocks. Waist to hip ratio was calculated by dividing waist circumference (cm) by hip circumference (cm). Waist to height ratio was calculated as waist circumference (cm) divided by height (cm). Weight (kg), BMI (weight in kg divided by square of height in metres) and body composition data (body fat percentage, fat mass, fat-free mass and trunk fat percentage) were estimated using a Tanita BC418MA segmental body composition analyser according to the manufacturer’s instructions. This device estimates body composition by bioimpedance analysis.
were further adjusted for BMI using the residual method.32 For this
associations of central adiposity measures and fat-free mass with risk
tus (never, past, current). For each covariate, missing values were
activity (low, moderate, high), parity (0, 1, 2, ≥3), age at menarche
contraceptive use (never, 0 to <5, 5 to <10, 10 to <15, ≥15 years), use of
The baseline characteristics of the 135 110 women according to quar-
tiles of BMI as measured at recruitment are shown in Table 1. Com-
measures were obtained from a linear regression of that variable on
BMI. These residuals (categorised into quartiles or standardised to SD
units) were investigated in relation to endometrial cancer risk in multi-
variable Cox models, which were additionally adjusted for BMI. The
effect of adjustment for fat mass (instead of BMI) on the association
of fat-free mass with risk of endometrial cancer was also evaluated.
To allow for comparison between any two groups, even if neither
is the referent category, the corresponding group-specific confidence
intervals (gCIs) for the HRs were calculated and presented in tables
and figures33; however, conventional 95% CIs are given in the texts.
The proportional hazard assumption was tested using log-log plots
and tests based on Schoenfeld residuals. To correct for regression
dilution bias, the HRs based on quartiles of body size/composition
variables were plotted against the repeat assessment mean values
within the same baseline categories.34 For HRs per 1-SD increase, the
log HRs and standard errors for the different measures were divided
by their respective regression dilution ratios (RDR), which were esti-
ated by regressing the repeat assessment values on the baseline
measures in the subset of the cohort with repeat assessment data.
Several sensitivity analyses were performed. First, we repeated all
analyses among never users of HRT, since HRT use is known to attenu-
ate the associations of adiposity with endometrial cancer risk.35 Sec-
ond, we assessed the associations of all measures of adiposity with
the risk of type I tumours, as it has been suggested that the aetiology
of type I and type II tumours may differ.36 There were too few cases
of type II tumours (n = 79) to allow for any meaningful analysis of
associations with this subtype. Third, to assess the potential impact of
missing data, we excluded participants with missing data on any of
the covariates. Fourth, we adjusted the associations of central adipos-
ity measures with endometrial cancer risk for BMI using the standard
method (ie, with BMI included as a covariate) instead of the residual
method. Lastly, we used standard categories for BMI (<25, 25 to <30,
30 to <35, ≥35 kg/m²), waist circumference (<80, 80 to <88, ≥88 cm)
and waist to hip ratio (<0.85, ≥0.85) to enable comparison with other
study populations.
All analyses were performed using STATA version 15.0.

3 | RESULTS
The baseline characteristics of the 135 110 women according to quar-
tiles of BMI as measured at recruitment are shown in Table 1. Com-
pared to women in the lowest quartile, women in the highest quartile
of BMI were more likely to be younger at menarche and to have a his-
tory of diabetes. They were less likely to be nulliparous, ever users of
contraceptive and current smokers. With the exception of height, the
mean values of all body size and body composition variables increased
in parallel with increasing BMI (Table 1). During a mean follow up of
6.8 years, 706 endometrial cancers were identified, with a mean
(SD) age at diagnosis of 65.5 (5.3) years.
The age-adjusted partial correlation coefficients (r) between the
various measures of body size and composition are shown in Table 2.
BMI was positively correlated with weight, body fat percentage, fat
mass and measures of central adiposity, with correlation coefficients ($r$) ranging from 0.45 for waist to hip ratio to 0.94 for fat mass. Waist to hip ratio showed weak to moderate correlations with other adiposity measures ($r < .45$), with the exception of waist circumference ($r = .74$) and waist to height ratio ($r = .74$). All bioimpedance-derived measures of adiposity were highly correlated with each other ($r > .80$).

Fat-free mass was correlated with BMI ($r = .69$) and to varying extents with other measures of adiposity ($r > .25$). Height was not correlated with body fat percentage ($r = .01$), waist circumference ($r = .03$) or waist to hip ratio ($r = -.08$) but showed weak correlations with other measures of adiposity (Table 2). As expected, measures of central adiposity and fat-free mass that were adjusted for BMI (using the residual method) were not correlated with BMI ($r$ ranged from $-.0043$ for waist to height ratio to $0.0045$ for fat-free mass; data not shown).

Table 3 and Figure 1 show the HRs for the associations of height and overall adiposity measures with the risk of endometrial cancer. All
measures of overall adiposity were positively associated with risk of endometrial cancer in an approximately linear fashion ($P_{\text{trend}} < .001$). After adjusting for confounders, the HR (95% CIs) for the highest vs lowest quartile of BMI was 3.45 (2.71-4.40); the corresponding HRs for other overall adiposity measures were 3.73 (2.92-4.76) for weight, 3.70 (2.87-4.77) for body fat percentage and 4.03 (3.12-5.20) for fat mass. The HRs per 1-SD increase in BMI, weight, body fat percentage and fat mass were broadly comparable, being 1.71 (1.61-1.82), 1.70 (1.60-1.81) for height (cm) in quartiles

| Body size/composition measures | Range          | Median at resurvey | Number of incident cases | Minimally adjusted HR (95% gCl) | Multivariable-adjusted HR (95% gCI) | $\chi^2$ for multivariable-adjusted model |
|--------------------------------|----------------|--------------------|--------------------------|---------------------------------|-------------------------------------|----------------------------------------|
| Height (cm) in quartiles       |                |                    |                          |                                 |                                     |                                        |
| 1                              | 121.0 to <158.1| 155.0              | 205                      | 1.00 (0.87-1.15)                | 1.00 (0.87-1.15)                    |                                        |
| 2                              | 158.1 to <162.1| 160.0              | 199                      | 1.17 (1.02-1.35)                | 1.20 (1.04-1.38)                    |                                        |
| 3                              | 162.1 to <166.0| 164.0              | 148                      | 0.97 (0.83-1.14)                | 1.02 (0.86-1.18)                    |                                        |
| 4                              | 166.0 to 199.0 | 169.0              | 154                      | 1.07 (0.91-1.25)                | 1.11 (0.95-1.31)                    |                                        |
| $P_{\text{for trend}}$         | .86            | .86                |                          |                                 |                                     |                                        |
| HR (95% CI) per 1-SD increase  |                |                    |                          | 1.02 (0.95-1.10)                | 1.04 (0.96-1.12)                    | 264                                    |

Weight (kg) in quartiles

| Body fat (%) in quartiles       |               |                   |                          |                                |                                    |                                        |
|--------------------------------|----------------|--------------------|--------------------------|---------------------------------|-------------------------------------|----------------------------------------|
| 1                              | 16.0 to <23.6  | 22.0               | 88                       | 1.00 (0.81-1.23)                | 1.00 (0.81-1.24)                    |                                        |
| 2                              | 23.6 to <26.2  | 24.8               | 117                      | 1.37 (1.14-1.65)                | 1.36 (1.14-1.64)                    |                                        |
| 3                              | 26.2 to <29.7  | 27.7               | 165                      | 1.80 (1.55-2.10)                | 1.75 (1.50-2.04)                    |                                        |
| 4                              | 29.7 to 59.9   | 32.5               | 336                      | 3.81 (3.41-4.24)                | 3.45 (3.07-3.88)                    |                                        |
| $P_{\text{for trend}}$         | <.0001         | <.0001             |                          |                                 |                                     |                                        |
| HR (95% CI) per 1-SD increase  | 1.77 (1.67-1.88)|                   |                          | 1.70 (1.60-1.81)                | 499                                 |                                        |

BMI (kg/m²) in quartiles

| Body fat (%) in quartiles       |               |                   |                          |                                |                                    |                                        |
|--------------------------------|----------------|--------------------|--------------------------|---------------------------------|-------------------------------------|----------------------------------------|
| 1                              | 10.1 to 32.6   | 30.1               | 79                       | 1.00 (0.80-1.25)                | 1.00 (0.80-1.25)                    |                                        |
| 2                              | 32.6 to <37.2  | 35.5               | 123                      | 1.49 (1.25-1.78)                | 1.50 (1.25-1.78)                    |                                        |
| 3                              | 37.2 to <41.6  | 39.5               | 184                      | 2.25 (1.95-2.60)                | 2.22 (1.92-2.57)                    |                                        |
| 4                              | 41.6 to 69.8   | 44.3               | 320                      | 3.97 (3.56-4.44)                | 3.70 (3.29-4.16)                    |                                        |
| $P_{\text{for trend}}$         | <.0001         | <.0001             |                          |                                 |                                     |                                        |
| HR (95% CI) per 1-SD increase  | 2.00 (1.83-2.20)|                   |                          | 1.92 (1.75-2.11)                | 456                                 |                                        |

Fat mass (kg) in quartiles

| Body fat (%) in quartiles       |               |                   |                          |                                |                                    |                                        |
|--------------------------------|----------------|--------------------|--------------------------|---------------------------------|-------------------------------------|----------------------------------------|
| 1                              | 5.0 to <20.2   | 17.2               | 75                       | 1.00 (0.80-1.25)                | 1.00 (0.80-1.26)                    |                                        |
| 2                              | 20.2 to <25.4  | 23.0               | 108                      | 1.41 (1.17-1.70)                | 1.41 (1.17-1.70)                    |                                        |
| 3                              | 25.4 to <32.0  | 28.1               | 191                      | 2.48 (2.15-2.85)                | 2.43 (2.11-2.80)                    |                                        |
| 4                              | 32.0 to 97.4   | 37.0               | 332                      | 4.36 (3.91-4.86)                | 4.03 (3.59-4.52)                    |                                        |
| $P_{\text{for trend}}$         | <.0001         | <.0001             |                          |                                 |                                     |                                        |
| HR (95% CI) per 1-SD increase  | 1.80 (1.69-1.91)|                   |                          | 1.73 (1.63-1.85)                | 501                                 |                                        |

Note: Minimally adjusted models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score and UK region. Multivariable-adjusted models include all the variables defined above, plus use of HRT, smoking status, physical activity, parity, age at menopause, oral contraceptive use, age at menarche and diabetes status. Standard deviations for the body size/composition measures were as follows: 6.2 cm for height, 13.5 kg for weight, 5.0 for BMI, 6.7% for body fat percentage and 9.7 kg for fat mass. Each HR (95% CI) per 1-SD increase was corrected for regression dilution bias by dividing the log HR and SE by the regression dilution ratio (RDR). The RDRs for height, weight, BMI, body fat percentage and fat mass were 0.98, 0.93, 0.94, 0.87 and 0.91, respectively. Likelihood ratio $\chi^2$ statistics for the basic model (ie, model with all covariate but no body size/composition measure) = 263.
Results for analyses that excluded participants with missing data on any covariates were not materially different from that of the main analysis (Table S2). Similarly, restricting the analysis to postmenopausal never HRT users did not substantially alter the overall pattern of the associations (Table S3).

Table 5 shows the HRs for endometrial cancer risk by WHO categories of BMI, waist circumference and waist to hip ratio, both before and after adjustment for BMI. The majority of incident endometrial cancers in this cohort were type I tumours (~80%). In analyses restricted to this subtype, the associations of adiposity measures with risk were slightly strengthened but the overall pattern remained unchanged (Table S2). Similarly, restricting the analysis to postmenopausal never HRT users did not substantially alter the overall pattern of the associations (Table S3). Results for analyses that excluded participants with missing data on any covariates were not materially different from that of the main analysis (data not shown).

(1.60-1.81), 1.92 (1.75-2.11) and 1.73 (1.63-1.85), respectively. However, in terms of χ² statistics, BMI appeared to be the most informative marker (χ² statistics for BMI, weight, body fat percentage and fat mass were 509, 499, 456 and 501 respectively). Height was not related to the risk of endometrial cancer (P_trend > .50, Table 3).

All central adiposity measures (waist circumference, waist to hip ratio, waist to height ratio and trunk fat percentage) were also associated with an increased risk of endometrial cancer in an approximately linear fashion (P_trend < .0001, Table 4 and Figure 1). In models adjusted for all confounders (except BMI), the HRs for the highest vs lowest quartile of these measures were 3.67 (2.90-4.66) for waist circumference, 2.23 (1.78-2.80) for waist to hip ratio, 3.43 (2.73-4.30) for waist to height ratio and 2.64 (2.53-4.14) for trunk fat percentage. The HRs associated with a 1-SD increase in each of these measures were broadly comparable to that of BMI, but the χ² statistics for these models (which ranged from 321 for waist to hip ratio to 477 for waist circumference) were substantially lower than that of BMI (χ² = 509), suggesting that BMI is more informative than these measures. After adjustment for BMI, the associations of all measures of central adiposity with risk were attenuated, although there was suggestive evidence that waist circumference (HR per 1-SD increase = 1.08, 95% CI: 1.00-1.17) and waist to hip ratio (HR per 1-SD increase = 1.13, 95% CI: 1.01-1.26) remained associated with risk (Table 4). Sensitivity analyses that adjusted for BMI by including this variable as a covariate in the model (as opposed to the residual method) produced very similar results (Table S1).

Hip circumference and fat-free mass were also positively associated with endometrial cancer risk, with multivariable-adjusted HRs (95% CIs) of 2.89 (2.31-3.63) and 2.70 (2.16-3.37), respectively, for those in the highest vs the lowest quartile (P_trend < .001, Table 4). However, additional adjustment for BMI completely attenuated these associations (P_trend > .20; Table 4). Adjustment of the association between fat-free mass and endometrial cancer for fat mass (instead of BMI) produced similar results (P_trend = .20, data not shown).

(155 160 165 170)
| Body size/composition measures | Range | Median at resurvey | Number of incident cases | Minimally adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI) | Further adjusted for BMI HR (95% CI) | χ² for multivariable-adjusted model | χ² for BMI adjusted model |
|-------------------------------|-------|--------------------|--------------------------|-------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------|
| **Waist circumference (cm) in quartiles** |       |                    |                          |                               |                                     |                                     |                                    |                               |
| 1                             | 46.0 to <76.1 | 74.0               | 93                       | 1.00 (0.82-1.23)              | 1.00 (0.81-1.23)                   | 1.00 (0.86-1.16)                   |                                     |                               |
| 2                             | 76.1 to <83.1 | 82.0               | 108                      | 1.30 (1.08-1.57)              | 1.32 (1.09-1.59)                   | 0.84 (0.70-1.00)                   |                                     |                               |
| 3                             | 83.1 to <92.1 | 89.0               | 172                      | 1.95 (1.68-2.26)              | 1.95 (1.68-2.26)                   | 1.26 (1.09-1.45)                   |                                     |                               |
| 4                             | 92.1 to 166.0 | 100.0              | 333                      | 3.93 (3.53-4.39)              | 3.67 (3.27-4.13)                   | 1.21 (1.06-1.39)                   |                                     |                               |
| P for trend                   |       |                    |                          |                               |                                     |                                     |                                    |                               |
|                              | <.0001 | <.0001             | .005                      |                               |                                     |                                     |                                    |                               |
| HR (95% CI) per 1-SD increase |       |                    |                          | 1.87 (1.74-2.01)              | 1.80 (1.67-1.94)                   | 1.08 (1.00-1.17)                   | 477                                 | 513                           |
| **Hip circumference (cm) in quartiles** |       |                    |                          |                               |                                     |                                     |                                    |                               |
| 1                             | 62.0 to <96.1 | 94.0               | 105                      | 1.00 (0.83-1.21)              | 1.00 (0.82-1.21)                   | 1.00 (0.87-1.15)                   |                                     |                               |
| 2                             | 96.1 to <102.1 | 100.0              | 130                      | 1.15 (0.97-1.37)              | 1.14 (0.96-1.35)                   | 0.93 (0.79-1.09)                   |                                     |                               |
| 3                             | 102.1 to <108.1 | 105.0              | 154                      | 1.74 (1.49-2.04)              | 1.68 (1.44-1.97)                   | 0.97 (0.83-1.14)                   |                                     |                               |
| 4                             | 108.1 to 179.0 | 114.0              | 317                      | 3.23 (2.89-3.61)              | 2.89 (2.58-3.25)                   | 0.99 (0.85-1.14)                   |                                     |                               |
| P for trend                   |       |                    |                          | <.0001                        | <.0001                             | .985                               |                                    |                               |
| HR (95% CI) per 1-SD increase |       |                    |                          | 1.74 (1.64-1.85)              | 1.66 (1.56-1.78)                   | 1.00 (0.93-1.08)                   | 461                                 | 509                           |
| **Waist to hip ratio in quartiles** |       |                    |                          |                               |                                     |                                     |                                    |                               |
| 1                             | 0.48 to <0.78 | 0.77                | 121                      | 1.00 (0.84-1.20)              | 1.00 (0.83-1.20)                   | 1.00 (0.86-1.16)                   |                                     |                               |
| 2                             | 0.78 to <0.83 | 0.82                | 171                      | 1.32 (1.14-1.54)              | 1.35 (1.16-1.57)                   | 0.96 (0.81-1.13)                   |                                     |                               |
| 3                             | 0.83 to <0.88 | 0.85                | 169                      | 1.52 (1.31-1.77)              | 1.54 (1.32-1.79)                   | 1.15 (0.99-1.33)                   |                                     |                               |
| 4                             | 0.88 to 1.56  | 0.89                | 245                      | 2.37 (2.09-2.69)              | 2.23 (1.96-2.55)                   | 1.22 (1.06-1.41)                   |                                     |                               |
| P for trend                   |       |                    |                          | <.0001                        | <.0001                             | .021                               |                                    |                               |
| HR (95% CI) per 1-SD increase |       |                    |                          | 1.66 (1.48-1.85)              | 1.57 (1.40-1.76)                   | 1.13 (1.01-1.26)                   | 321                                 | 513                           |
| **Waist to height ratio in quartiles** |       |                    |                          |                               |                                     |                                     |                                    |                               |
| 1                             | 0.29 to <0.48 | 0.46                | 106                      | 1.00 (0.83-1.21)              | 1.00 (0.82-1.21)                   | 1.00 (0.86-1.16)                   |                                     |                               |
| 2                             | 0.48 to <0.52 | 0.51                | 95                       | 1.21 (0.99-1.48)              | 1.22 (1.00-1.49)                   | 1.11 (0.95-1.29)                   |                                     |                               |
| 3                             | 0.52 to <0.58 | 0.55                | 176                      | 1.75 (1.51-2.03)              | 1.76 (1.52-2.03)                   | 0.99 (0.85-1.16)                   |                                     |                               |
| 4                             | 0.58 to 1.03  | 0.63                | 329                      | 3.69 (3.30-4.12)              | 3.42 (3.04-3.86)                   | 1.15 (1.00-1.32)                   |                                     |                               |
| P for trend                   |       |                    |                          | <.0001                        | <.0001                             | .342                               |                                    |                               |
| HR (95% CI) per 1-SD increase |       |                    |                          | 1.83 (1.71-1.97)              | 1.76 (1.64-1.90)                   | 1.03 (0.95-1.11)                   | 463                                 | 509                           |
| Trunk fat (%) in quartiles    |       |                    |                          |                               |                                     |                                     |                                    |                               |

(Continues)
**TABLE 4** (Continued)

| Body size/composition measures | Range       | Median at resurvey | Number of incident cases | Minimally adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI) | Further adjusted for BMI HR (95% CI) | $\chi^2$ for multivariable-adjusted model | $\chi^2$ for BMI adjusted model |
|-------------------------------|-------------|---------------------|--------------------------|--------------------------------|-----------------------------------|----------------------------------------|----------------------------------------|-------------------------------|
| 1                            | 3.0 to <29.7| 26.8                | 85                       | 1.00 (0.81-1.24)               | 1.00 (0.81-1.24)                   | 1.00 (0.86-1.17)                          |                                       |                               |
| 2                            | 20.7 to <34.9| 33.1                | 121                      | 1.39 (1.16-1.66)               | 1.38 (1.16-1.65)                   | 1.07 (0.92-1.24)                          |                                       |                               |
| 3                            | 34.9 to <39.7| 37.2                | 200                      | 2.33 (2.03-2.68)               | 2.29 (1.99-2.63)                   | 1.10 (0.94-1.28)                          |                                       |                               |
| 4                            | 39.7 to 75.6| 42.1                | 300                      | 3.47 (3.09-3.89)               | 3.24 (2.88-3.65)                   | 1.21 (1.04-1.41)                          |                                       |                               |
| $P$ for trend                 |              |                     |                          | <.0001                         | <.0001                            | .087                                    |                                       |                               |
| HR (95% CI) per 1-SD increase |             |                     |                          | 1.87 (1.70-2.05)               | 1.79 (1.63-1.97)                   | 1.06 (0.97-1.16)                          | 405                                    | 510                           |

| Fat-free mass (kg) in quartiles | Range       | Median at resurvey | Number of incident cases | Minimally adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI) | Further adjusted for BMI HR (95% CI) | $\chi^2$ for multivariable-adjusted model | $\chi^2$ for BMI adjusted model |
|---------------------------------|-------------|---------------------|--------------------------|--------------------------------|-----------------------------------|----------------------------------------|----------------------------------------|-------------------------------|
| 1                               | 26.2 to <40.7| 38.5                | 110                      | 1.00 (0.83-1.21)               | 1.00 (0.83-1.21)                   | 1.00 (0.86-1.16)                          |                                       |                               |
| 2                               | 4.7 to <43.5 | 41.4                | 123                      | 1.17 (0.98-1.39)               | 1.16 (0.97-1.39)                   | 1.06 (0.91-1.24)                          |                                       |                               |
| 3                               | 43.5 to <46.7| 44.2                | 170                      | 1.65 (1.42-1.91)               | 1.59 (1.37-1.85)                   | 1.12 (0.97-1.30)                          |                                       |                               |
| 4                               | 46.7 to 81.7| 48.0                | 303                      | 3.02 (2.70-3.39)               | 2.70 (2.40-3.04)                   | 1.06 (0.98-1.14)                          | 417                                    | 511                           |
| $P$ for trend                   |              |                     |                          | <.0001                         | <.0001                            | .258                                    |                                       |                               |
| HR (95% CI) per 1-SD increase   |              |                     |                          | 1.68 (1.57-1.79)               | 1.58 (1.48-1.69)                   | 1.06 (0.98-1.14)                          |                                       |                               |

Note: Minimally adjusted models stratified by year of birth and year of recruitment and adjusted for age, deprivation score and region. Multivariable-adjusted models include all the variables defined above, plus use of HRT, smoking status, physical activity, parity, age at menopause, oral contraceptive use, age at menarche and diabetes status. Standard deviations for the body size/composition measures were as follows: 12.3 cm for waist circumference, 10.1 cm for hip circumference, 0.07 for waist to hip ratio, 0.08 for waist to height ratio and 7.6% for trunk fat percentage and 4.8 kg for fat-free mass. Each HR (95% CI) per 1-SD increase was corrected for regression dilution bias by dividing the log HR and SE by the regression dilution ratio (RDR). The RDRs for waist circumference, hip circumference, waist to hip ratio, waist to height ratio, trunk fat percentage and fat-free mass were 0.87, 0.89, 0.63, 0.88, 0.83 and 0.91, respectively. Likelihood ratio $\chi^2$ statistics for the basic model (ie, model with all covariate but no body size/composition measure) = 263.

$*$This column shows the HRs for endometrial cancer by quartiles (or per 1-SD units) of residuals generated from regression of central adiposity measures/fat-free mass on BMI. The values provided for range, median at resurvey and incident cases (columns 2, 3 and 4) do not apply to this column.
In this large prospective cohort, endometrial cancer risk was positively associated with all measures of overall adiposity (BMI, weight, body fat percentage and fat mass) and central adiposity (waist circumference, waist to hip ratio, waist to height ratio and trunk fat percentage). The magnitudes of associations (per 1-SD increment) were broadly comparable across the different indices of adiposity; however, in terms of \( \chi^2 \) statistics of the models, BMI appeared to be the most informative measure. The positive associations between measures of central adiposity and endometrial cancer risk were substantially attenuated after adjusting for BMI, but waist circumference and waist to hip ratio remained marginally associated with risk. Hip circumference and fat-free mass were not associated with endometrial cancer risk independent of BMI in our study. Height was not a predictor of endometrial cancer risk in our study population.

BMI is the most commonly used measure of adiposity in studies relating adiposity to risk of endometrial cancer. There is limited data on the association of more specific measures of body fat (such as body fat percentage and fat mass) with risk. Our finding of a strong positive association between body fat percentage and endometrial cancer is consistent with that found in the China Kadoorie Biobank, where risk increased by 58% for each 1-SD increase in body fat percentage (that was also measured by bioimpedance).37 Greater fat mass was also associated with an increased risk of endometrial cancer. Although both body fat percentage and fat mass are more precise measures of overall adiposity than BMI, the results of our study suggest that they are not better indicators of endometrial cancer risk.

Previous prospective studies examining the independent effect of central adiposity on endometrial cancer risk have reported conflicting results.12-20 In the California Teachers’ Study, waist circumference and waist to hip ratio were positively associated with endometrial cancer risk after adjustment for BMI.17 In contrast, the Nurses’ Health Study did not report an independent association with these measures,14 while the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort reported an independent association with waist circumference but not waist to hip ratio.37 A 2015 meta-analysis also found an independent association with waist circumference but not waist to hip ratio.5 One study that used Mendelian randomisation found no evidence to support an association between waist to hip ratio and endometrial cancer risk.38 In the present analysis, a small increase in risk remained for waist circumference and waist to hip ratio after adjusting for BMI, suggesting that central adiposity as reflected by these measures may confer risk above and beyond overall adiposity.

Hip circumference was not an independent predictor of endometrial cancer risk in our study, which is consistent with results from the EPIC cohort.19 the Nurses’ Health Study14 and the Black Women’s Health Study.13 Height was also unrelated to endometrial cancer risk here, which is consistent with results from some studies12,19,26-28 but not others.22-25 Fat-free mass, which reflects viscera, bone and muscle mass, was positively associated with risk of endometrial cancer but this association disappeared after adjustment for BMI.

Several mechanisms have been proposed to explain the positive association between adiposity and endometrial cancer risk in post-menopausal women. The predominant hypothesis is that adiposity promotes oestrogen-driven proliferation of endometrial cells by elevating circulating levels of oestrogen through increased aromatisation of androgen to oestrone in the adipose tissue.39,40 Adiposity, particularly central adiposity, is also associated with insulin resistance, characterised by elevated levels of insulin. Insulin could promote endometrial carcinogenesis directly through its proliferative effect

### TABLE 5 Hazard ratios (95% gsCI) for endometrial cancer by WHO categories for BMI, waist circumference and waist to hip ratio

| Adiposity measures          | Number of incident cases | Multivariable-adjusted model HR (95% gsCI) | Further adjusted for BMI* HR (95% gsCI) |
|-----------------------------|--------------------------|------------------------------------------|----------------------------------------|
| **BMI (kg/m\(^2\))**        |                          |                                          |                                        |
| <25                         | 141                      | 1.00 (0.84-1.19)                         | –                                      |
| 25 to <30                    | 239                      | 1.64 (1.44-1.86)                         | –                                      |
| 30 to <35                    | 149                      | 2.46 (2.10-2.89)                         | –                                      |
| ≥35                         | 177                      | 5.92 (5.05-6.94)                         | –                                      |
| **P for trend**              |                          | <.0001                                   |                                        |
| **Waist circumference (cm)**|                          |                                          |                                        |
| <80                         | 134                      | 1.00 (0.84-1.19)                         | 1.00 (0.83-1.21)                       |
| 80 to <88                    | 141                      | 1.48 (1.26-1.75)                         | 1.13 (0.97-1.30)                       |
| ≥88                         | 431                      | 2.99 (2.70-3.31)                         | 1.37 (1.15-1.60)                       |
| **P for trend**              |                          | <.0001                                   | .015                                   |
| **Waist to hip ratio**b      |                          | Reference                                | Reference                              |
| <0.85                       | 366                      | 1.58 (1.38-1.84)                         | 1.10 (0.93-1.29)                       |
| ≥0.85                       | 340                      | Reference                                | Reference                              |

Note: Models were stratified by year of birth and year of recruitment, and adjusted for age, deprivation score, UK region, parity, use of HRT, smoking status, physical activity, age at menopause, oral contraceptive use, age at menarche and diabetes.

*Adjusted for BMI (continuous variable) using the standard method that is, BMI included as a covariate in the model.

**HR (95% CI) presented for waist to hip ratio.

4 | DISCUSSION

In this large prospective cohort, endometrial cancer risk was positively associated with all measures of overall adiposity (BMI, weight, body fat percentage and fat mass) and central adiposity (waist circumference, waist to hip ratio, waist to height ratio and trunk fat percentage). The magnitudes of associations (per 1-SD increment) were broadly comparable across the different indices of adiposity; however, in terms of \( \chi^2 \) statistics of the models, BMI appeared to be the most informative measure. The positive associations between measures of central adiposity and endometrial cancer risk were substantially attenuated after adjusting for BMI, but waist circumference and waist to hip ratio remained marginally associated with risk. Hip circumference and fat-free mass were not associated with endometrial cancer risk independent of BMI in our study. Height was not a predictor of endometrial cancer risk in our study population.

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or indirectly by increasing bioavailability of oestrogen and insulin-like growth factor-1 (IGF-1). Adiposity may also influence endometrial cancer risk by decreasing the circulating levels of adiponectin, which protects against the risk of endometrial cancer. Obesity-induced low-grade chronic inflammation may also mediate this association.

The strengths of our study include its large size, prospective design and breadth of data on body size and composition, all of which were measured rather than self-reported, thereby minimising potential for differential misclassification, which has been particularly shown for self-reported body weight and height. Repeat measures available in a subset of the cohort allowed for assessment of the extent of measurement error (quantified by RDRs) associated with each measure and the correction of risk estimates for regression dilution bias. With the exception of waist to hip ratio, the RDRs for the body size/composition indices were small, suggesting that these measures did not change substantially over a 5-year period.

Several limitations of our study need to be considered. The associations between body size/composition variables and endometrial cancer risk reported in our study largely reflect associations with type I tumours, which account for majority of the incident cases (~80%). The small number of type II tumours precluded analysis of associations with this subtype. Participants in UK Biobank were predominantly of European origin; therefore, the results of our study may not be generalisable to other ethnic group. Missing values for each covariate were assigned to a separate category to prevent loss of data. This method of handling missing data has limitations, including the possibility of producing biased results due, at least in part, to incomplete adjustment for confounders. However, results from a sensitivity analysis that excluded participants with missing data on any covariate were not appreciably different from that of the main analysis.

Body composition parameters in our study were estimated by bio-impedance analysis, which is a valid technique for estimating body composition. Unlike imaging techniques such as dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI) that measure body composition with high precision, bioimpedance measures the resistance/impedance of body tissues to a small alternating current and uses the impedance readings in a predictive equation to estimate various body fractions. The accuracy of bioimpedance-derived measurements of body composition depends on several factors including hydration status, presence of medical conditions that may impact fluid and electrolyte balance and the prediction equation used. Prediction equations are often population-specific as they describe the empirical relationship between impedance and body composition estimated by reference methods in a given population. In the present analysis, estimates of body composition were based on prediction equations incorporated into the software of the Tanita BC418MA body composition analyser, which may not best represent the UK Biobank cohort. Plans are, however, under way to validate bioimpedance-derived measures of body composition against MRI and DEXA scans currently being taken in a large subset of this cohorts.

In summary, BMI, body fat percentage and fat mass showed similar associations with endometrial cancer risk. Central adiposity, as reflected by waist circumference and waist to hip ratio, may be associated with endometrial cancer risk independently of BMI, but this requires further investigation.

ACKNOWLEDGEMENTS

We would like to thank the participants and staff of UK Biobank for their valuable contribution.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA ACCESSIBILITY

Further details on UK Biobank including data availability and access procedures are provided on the study website (https://www.ukbiobank.ac.uk/). This analysis was performed under the UK Biobank Application Number 8294 and the code used to generate these results has been returned to UK Biobank.

ETHICS STATEMENT

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee and all participants provided informed consent at recruitment.

ORCID

Wemimo Omiyale https://orcid.org/0000-0002-0124-2939

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Omiyale W, Allen NE, Sweetland S. Body size, body composition and endometrial cancer risk among postmenopausal women in UK Biobank. Int. J. Cancer. 2020;147:2405–2415. https://doi.org/10.1002/ijc.33023