Association of Oophorectomy and Fat and Lean Body Mass: Evidence from a Population-Based Sample of U.S. Women

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ABSTRACT

Background: Bilateral oophorectomy during a nonmalignant hysterectomy is frequently performed for ovarian cancer prevention in premenopausal women. Oophorectomy before menopause leads to an abrupt decline in ovarian hormones that could adversely affect body composition. We examined the relationship between oophorectomy and whole-body composition.

Methods: Our study population included cancer-free women 35 to 70 years old from the 1999–2006 National Health and Nutrition Examination Survey, a representative sample of the U.S. population. A total of 4,209 women with dual-energy x-ray absorptiometry scans were identified, including 445 with hysterectomy, 552 with hysterectomy and oophorectomy, and 3,212 with no surgery. Linear regression was used to estimate the difference in total and regional (trunk, arms, and legs) fat and lean body mass by surgery status.

Results: In multivariable models, hysterectomy with and without oophorectomy was associated with higher total fat mass [mean percent difference (β); $\beta_{oophorectomy}$: 1.61%; 95% confidence interval (CI), 1.00–2.28; $\beta_{hysterectomy}$: 0.88%; 95% CI, 0.12–1.58] and lower total lean mass [$\beta_{oophorectomy}$: −1.48%; 95% CI, −2.67, −1.15; $\beta_{hysterectomy}$: −0.87%; 95% CI, −1.50, −0.24) compared with no surgery. Results were stronger in women with a normal body mass index (BMI) and those <45 years at surgery. All body regions were significantly affected for women with oophorectomy, whereas only the trunk was affected for women with hysterectomy alone.

Conclusions: Hysterectomy with oophorectomy, particularly in young women, may be associated with systemic changes in fat and lean body mass irrespective of BMI.

Impact: Our results support prospective evaluation of body composition in women undergoing hysterectomy with oophorectomy at a young age.

Introduction

Many average-risk women undergo bilateral oophorectomy for ovarian cancer prevention at the time of a nonmalignant hysterectomy. Hysterectomy is the most common nonobstetric gynecologic surgery in the United States, with about 500,000 performed annually (1). Over 90% of all hysterectomies are performed for nonmalignant gynecologic conditions such as uterine fibroids, abnormal uterine bleeding, and endometriosis. It is estimated that a bilateral oophorectomy is performed in 46% to 52% of all hysterectomies, both for nonmalignant gynecologic conditions and cancer prevention (2, 3). Bilateral oophorectomy during a nonmalignant hysterectomy is performed in 31% of women <45 years, 59% of women 45 to 49 years, and 74% of women ≥50 years (3). In addition, women at high risk of ovarian cancer, such as *BRCA1/2* carriers, are counseled to undergo prophylactic oophorectomy after childbearing or between 35 and 40 years (4). Despite the high prevalence of these surgeries, the long-term health effects of oophorectomy remain poorly understood.

Prior studies have found an increased incidence of cardiovascular disease (5, 6), cognitive decline and dementia (7), and increased all-cause and cardiovascular disease mortality (8, 9) after oophorectomy. Oophorectomy, particularly in premenopausal women, has also been linked to increased adiposity, measured by body mass index (BMI), waist circumference, and skinfold thickness (10–12). To our knowledge, no prior studies have examined the association of oophorectomy and objectively measured total and regional fat and lean body mass.

Body fat is a more sensitive marker of adiposity, and it can vary considerably even among individuals with the same BMI or weight. Excess body fat is an established risk factor for cancer and cardiovascular disease independent of BMI (13–15). In addition, there is growing evidence that adequate lean mass is beneficial for overall health, and loss of lean mass or sarcopenia is associated with physical disability and mortality in older adults (16, 17).

Changes that occur during natural menopause, such as increased systemic inflammation (18, 19), increased glucose and insulin levels (20), and increased proinflammatory cytokine levels (21, 22), appear to be accelerated in women who undergo premenopausal oophorectomy due to the abrupt decline in endogenous estrogen and androgen. These hormonal changes have also been implicated in the gain of fat mass and loss of lean mass (23).

The objective of this study was to examine the association of oophorectomy with total and regional fat and lean body mass measured using dual-energy x-ray absorptiometry (DXA) scans. DXA scans are considered the gold standard for body composition assessment and the most accurate way to measure fat and lean body mass (24–26). Because oophorectomy is commonly performed at the time of hysterectomy, we compared total and regional fat and lean body mass in women who reported hysterectomy with oophorectomy and hysterectomy alone with women with intact ovaries and uterus (no surgery).

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

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Materials and Methods

Study population

Data were drawn from the National Health and Nutrition Examination Survey (NHANES), a population-based cross-sectional survey that uses stratified, multistage probability sampling to produce nationally representative estimates of the civilian, noninstitutionalized U.S. population. The protocols for the conduct of NHANES were approved by the Institutional Review Board of the National Center for Health Statistics, and all participants provided written informed consent prior to data collection. This study was deemed exempt by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health as the data used were deidentified. The study was conducted in accordance with recognized ethical guidelines (U.S. Common Rule).

The current study used four cycles of NHANES data from 1999 to 2006. The study sample was restricted to women 35 to 70 years old who completed both the interview and medical examination and had DXA measurements ($n = 5{,}225$). A minimum age of 35 years was used as few women younger than 35 years undergo oophorectomy and women over 70 years were excluded because studies have shown a more rapid decline in lean mass after age 70 (27, 28).

The reproductive health questionnaire was used to ascertain history of gynecologic surgery. Women were excluded if they were missing age at surgery ($n = 4$), height and weight at DXA scan ($n = 170$), or weight at age 25 ($n = 205$). Women were also excluded if they reported removal of one ovary at the time of hysterectomy ($n = 299$) and had oophorectomy without hysterectomy ($n = 57$). Women with a history of reproductive cancers (breast, $n = 118$; cervical, $n = 81$; uterine, $n = 50$; ovarian, $n = 32$) were also excluded. After exclusions, 4,209 women were included in the analytic sample, 3,212 without surgery (intact ovaries and uterus), 445 with hysterectomy, and 552 with hysterectomy and oophorectomy. For brevity, oophorectomy will denote hysterectomy with bilateral oophorectomy for the rest of the article.

Assessment of body composition

Whole-body DXA scans were used to ascertain total and regional fat and lean body mass. Scans were performed during the medical examination using a Hologic QDR 4500A fan beam x-ray bone densitometer (Hologic, Inc.) and reviewed for quality control using Hologic Discovery software, version 12.1. About 20% of DXA scans were deemed invalid and coded as missing data. All missing data were imputed by NHANES using sequential regression multivariate imputation (29). Five data files containing both the nonmissing and imputed DXA data were provided. Continuous measurements were provided for total and regional (arms, trunk, and legs) fat mass and total and regional lean mass excluding bone mineral content (30). DXA values were also categorized into tertiles to classify women into low (T1), moderate (T2), and high (T3) fat and lean body mass. Tertile cut points were based on the distribution of fat and lean mass among women without surgery (Supplementary Table S1). A high total fat mass and low total lean mass body composition variable was created by jointly classifying women with high total fat mass (T3) and low total lean mass (T1).

Covariates

Information on demographics and lifestyle factors, including age, sex, race, education, income, smoking, physical activity, cigarette/tobacco use, weight history, and reproductive history, was based on the in-person interview conducted before the medical examination. Alcohol consumption was categorized as ≥12 drinks in the past year or <12 drinks in the past year. In addition, respondents were asked to estimate the average number of alcoholic drinks they consumed per day in the past year. Smoking was categorized as never, former, and current. Physical activity over the past month, including exercise, sports, and physically active hobbies, was categorized as none, moderate, and vigorous. Moderate physical activity was defined as activities for at least 10 minutes that cause light sweating or slight-to-moderate increases in breathing or heart rate, and vigorous physical activity was defined as activities for at least 10 minutes that cause heavy sweating or large increases in breathing or heart rate. Age at surgery was categorized as <45 and ≥45 years. This cut point was selected as most women were likely to be premenopausal at 45 (31) and to allow comparability with prior studies (5, 8, 32–34). Parity was classified as parous or nulliparous, and postsurgery estrogen replacement therapy (ERT) use was classified as yes if women reported use of estrogen after surgery and no otherwise. History of endometriosis and uterine fibroids was classified based on prior physician diagnosis. Body weight and height were measured during the medical examination. BMI was calculated from measured height and weight and categorized as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2).

Statistical analyses

Characteristics of women with and without surgery were compared using t tests for continuous variables and χ^2 tests for categorical variables. Linear regression models were used to estimate the mean difference in percent fat and lean body mass by surgery status. Distributions of total and regional fat and lean mass were examined graphically, and no departures from normality were observed. Multinomial logistic regression models were utilized to estimate the odds ratio (OR) of being in the middle versus the lowest tertile (T2 vs. T1) and the highest versus the lowest tertile (T3 vs. T1) by surgery status. Results were reported overall and by age at surgery. Effect modification by age at DXA scan, race, and BMI at DXA scan was evaluated by adding cross-product terms to the regression model. Age-adjusted prevalence of high total fat and low total lean body mass was calculated overall, by age at surgery, by physical activity, and by postsurgery ERT use. All analyses were weighted to account for the complex survey design and produce results generalizable to the U.S. population. Standard errors were obtained using the Taylor series (linearization) method.

Models were adjusted for age at DXA scan, race, income, physical activity, smoking, education, alcohol use, oral contraceptive use, BMI at age 25, and postsurgery ERT use. Sensitivity analyses were performed by additionally adjusting for total number of calories consumed from a 24-hour dietary recall, excluding women who reported postsurgery ERT use, excluding women with a diagnosis of uterine fibroids and endometriosis, and limiting the analysis to women with a history of hysterectomy with and without oophorectomy.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc.) and Stata version 14.2 (Stata Corporation). Analyses were run separately on each imputed dataset provided by NHANES, and the resulting estimates were combined to produce a single estimate.

Results

Table 1 summarizes the characteristics of the 4,209 women by history of hysterectomy with and without oophorectomy. Women with a history of surgery were older at DXA scan, less likely to have a college education, and more likely to have an annual family income of <$20,000 compared with women without surgery. Women with oophorectomy were more likely to be non-Hispanic white compared

Table 1. Characteristics of the study population by hysterectomy and oophorectomy status.

	No surgery ($n = 3,212$)	Hysterectomy ($n = 445$)	Hysterectomy and oophorectomy ($n = 552$)	*P* value
Age at DXA scan, years, mean (SD)	48.2 (7.2)	53.8 (7.8)	54.4 (7.4)	<0.001
Age at surgery, years, mean (SD)	N/A	38.3 (6.2)	40.6 (6.2)	N/A
Race, %				
Non-Hispanic White	71.4	71.0	80.8	
Non-Hispanic Black	10.8	13.9	10.9	
Mexican American	6.3	4.0	2.9	
Other	11.5	11.1	5.4	<0.001
Highest education, %				
High school or less	38.3	49.3	51.7	
Some college or above	57.9	48.5	45.4	
Missing	3.7	2.2	3.0	<0.001
Annual family income, %				
<$20,000	17.8	21.3	22.9	
≥$20,000	80.1	77.1	73.6	
Missing	2.1	1.6	3.5	0.024
Smoking status, %				
Never	56.0	54.5	48.9	
Former	22.9	24.6	23.6	
Current	21.1	20.9	27.5	0.073
Parous, %	94.9	94.2	97.9	0.126
Diagnosed with endometriosis, %	4.0	8.5	21.7	<0.001
Diagnosed with uterine fibroids, %	9.7	22.6	24.6	<0.001
Oral contraceptive use, %	72.0	74.7	74.9	0.423
BMI at DXA scan, %				
Underweight	1.7	0.7	1.6	
Normal	34.7	30.5	25.9	
Overweight	27.8	25.8	30.4	
Obese	35.8	43.0	42.1	0.020
BMI at age 25, %				
Underweight	8.9	9.2	10.8	
Normal	71.8	70.9	72.7	
Overweight	12.4	11	9.6	
Obese	6.9	8.9	6.9	0.268
Number of drinks per week over past year, mean (SD)	2.0	1.8	1.8	0.184
Physical activity over past 30 days, %				
None	36.2	45.6	40.2	
Moderate	32.2	34.5	38.1	
Vigorous	31.6	19.9	21.8	<0.001
Postsurgery ERT, %	N/A	21.9	66.4	N/A

Abbreviations: BMI, body mass index; DXA, dual-energy x-ray absorptiometry; ERT, estrogen replacement therapy; N/A, not applicable; SD, standard deviation.

with women without surgery, whereas women with hysterectomy alone were more likely to be non-Hispanic Black. Women with a history of oophorectomy were older at the time of surgery compared with those with a history of hysterectomy alone. A higher proportion of women with surgery reported a diagnosis of endometriosis and uterine fibroids compared with women without surgery. There were no differences in parity, oral contraceptive use, alcohol consumption, and smoking between the groups. About 66% of women with oophorectomy and 22% of women with hysterectomy reported postsurgery ERT use. Women with a history of surgery were more likely to be obese at DXA scan and report no physical activity compared with women without surgery. BMI at age 25 (prior to surgery) did not differ between the groups.

Total fat and lean body mass

After adjusting for age, race, income, physical activity, smoking, education, alcohol use, oral contraceptive use, BMI at age 25, and postsurgery ERT use, women with oophorectomy had on average 1.61% [95% confidence interval (CI), 1.00%–2.28%) higher total fat mass and 1.48% (95% CI, -2.14%, -0.82%) lower total lean mass compared with women without surgery. In models stratified by age at surgery, associations were stronger and only statistically significant in women who had oophorectomy <45 years (β_{fat}: 2.09%, 95% CI, 1.28%–2.91%; β_{lean}: −1.90%, 95% CI, −2.67%, −1.15%). Similarly, women with hysterectomy alone had 0.88% (95% CI, 0.12%–1.58%) higher total fat mass and 0.87% (95% CI, −1.50%, −0.24%) lower total lean mass compared with women without surgery. Associations were stronger and only statistically significant in women who had hysterectomy <45 years (β_{fat}: 1.00%, 95% CI, 0.23%–1.75%; β_{lean}: −0.92%, 95% CI: −1.63%, −0.21%; **Fig. 1**).

Next, we evaluated the impact of age (<45 and ≥45 years) and BMI (<25 and ≥25 kg/m^2) at DXA scan on the association between hysterectomy with and without oophorectomy and total fat and lean mass. We did not evaluate race as it was not a significant effect measure

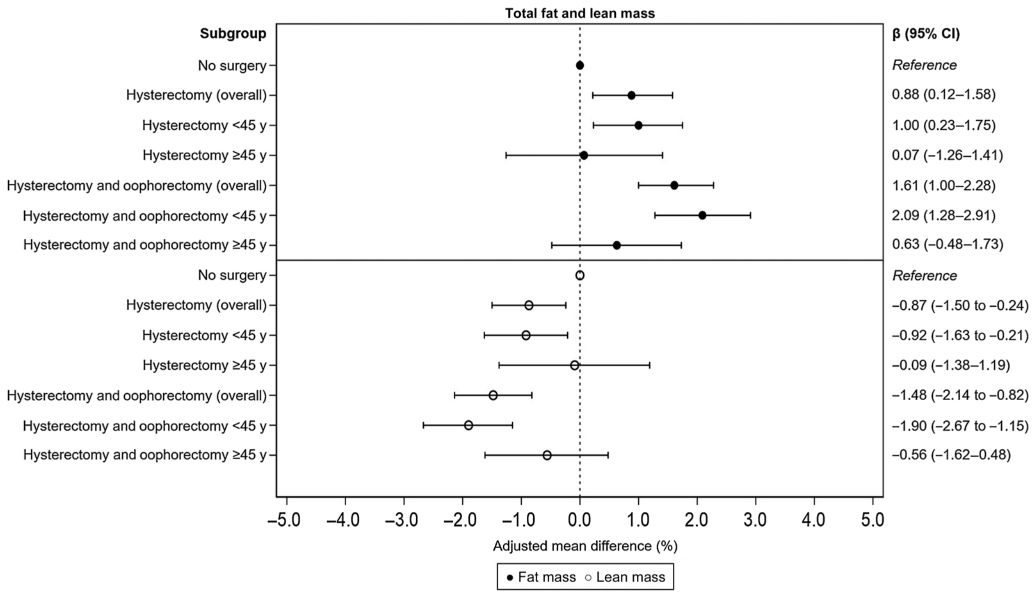

Figure 1.

Multivariable-adjusted mean percent difference and 95% CI for total fat and lean mass by hysterectomy and oophorectomy status, overall and by age at surgery. Adjusted for age at interview, race, smoking, alcohol use, education, BMI at age 25, parity, oral contraceptive use, and postsurgery ERT use.

modifier. Among women <45 years at DXA scan, the median time since surgery was 6 years [interquartile range (IQR), 2–10 years] for oophorectomy and 5 years (IQR, 2–11 years) for hysterectomy alone. Among women ≥45 years at DXA scan, the median time since surgery was 16 years (IQR, 7–23 years) for oophorectomy and 19 years (IQR, 12–26 years) for hysterectomy alone. Regardless of age at DXA scan, oophorectomy was associated with a significant increase in total fat mass and decrease in total lean mass with the greatest difference in the subgroup of women <45 years at DXA scan (β_{fat}: 3.25%, 95% CI, 1.03%–5.54%; β_{lean}: −2.86%, 95% CI, −5.00%, −1.07%). A similar pattern was noted for hysterectomy alone, although the beta estimates were smaller when compared with oophorectomy (β_{fat}: 1.33%, 95% CI, 0.00%–2.66%; β_{lean}: −1.22%, 95% CI, −2.47%, 0.03%; **Table 2**).

The association between oophorectomy and total fat and lean mass persisted regardless of BMI at DXA scan. Of note, the increase in fat mass and decrease in lean mass by oophorectomy history was stronger in women with BMI < 25 kg/m^2 at DXA scan. There was no statistically significant association between hysterectomy alone and total fat and lean mass in models stratified by BMI at DXA scan (**Table 3**).

Regional fat and lean body mass

Women with oophorectomy had on average 2.27% (95% CI, 1.40%–3.13%) higher trunk fat mass and 2.18% (95% CI, −3.03%, −1.34%) lower trunk lean mass compared with women without surgery, with stronger associations among women with oophorectomy <45 years (β_{fat}: 2.95%, 95% CI, 1.92%–3.99%; β_{lean}: −2.85%, 95% CI, −3.85%, −1.84%). Women with hysterectomy had 1.42% (95% CI, 0.45%–2.40%) higher trunk fat mass and 1.38% (95% CI, −2.33%, −0.44%) lower trunk lean mass compared with women without surgery, with stronger associations among women with hysterectomy <45 years (β_{fat}: 1.47%, 95% CI, 0.41%–2.54%; β_{lean}: -1.44%, 95% CI, −2.47%, -0.40%; **Fig. 2**). Significant differences in arms and legs fat and lean mass were only observed for women with oophorectomy (Supplementary Figs. S1 and S2).

In analyses stratified by age at DXA scan, the increase in regional fat mass and decrease in regional lean mass were stronger in the subgroup of women <45 years at DXA scan (**Table 2**). In analyses stratified by BMI at DXA scan, the association between oophorectomy and regional fat and lean mass was stronger in women with BMI <25 kg/m^2 at DXA scan. A similar pattern was noted for hysterectomy alone with respect to trunk fat and lean mass, although the β estimates were smaller when compared with oophorectomy. There was no statistically significant association between hysterectomy alone and arms and legs fat and lean mass in BMI-stratified analyses (**Table 3**).

Sensitivity analyses

Results were unchanged with additional adjustment for total caloric intake, and when women who reported postsurgery ERT use and women with a diagnosis of endometriosis and uterine fibroids were excluded (Supplementary Table S2). In analyses limited to women with a history of prior surgery, no significant differences were noted in total and regional fat and lean body mass in women with oophorectomy compared with women with hysterectomy alone (Supplementary Table S3). Results were similar for multinomial logistic regression models based on tertile cut points (Supplementary Table S4).

Prevalence of high total fat and low total lean body mass

The age-adjusted prevalence of high total fat and low total lean body mass by hysterectomy and oophorectomy status is shown in **Fig. 3**. Compared with women without surgery (30.9%, 95% CI, 28.6%–33.2%), the prevalence of high total fat and low total lean mass was higher in women with oophorectomy (41.2%, 95% CI, 36.6%–45.7%) and hysterectomy alone (35.1%, 95% CI, 29.7%–40.4%), particularly those <45 years at the time of surgery (oophorectomy, 45.3%, 95% CI, 40.6%–49.8%; hysterectomy alone, 36.7%, 95% CI, 30.7%–42.5%).

Among women with a history of oophorectomy, a significantly lower prevalence of high total fat and low total lean mass was observed in women who reported vigorous physical activity (32.3%, 95% CI,

Table 2. Multivariable-adjusted mean percent difference and 95% CI for total and regional fat and lean body mass by hysterectomy and oophorectomy status and age at DXA scan[a].

		Age < 45 y (n = 1,365)			Age ≥ 45 y (n = 2,844)		
DXA measure	Subgroup	n	β (95% CI)	P value	n	β (95% CI)	P value
Total fat mass	No surgery	1,227	Reference		1,985	Reference	
	Hysterectomy	68	1.33 (0.00–2.66)	0.051	377	0.76 (0.02–1.51)	0.046
	Hysterectomy and oophorectomy	70	3.25 (1.03–5.54)	0.005	482	1.29 (0.56–2.01)	<0.001
Total lean mass	No surgery	1,227	Reference		1,985	Reference	
	Hysterectomy	68	−1.22 (−2.47, 0.03)	0.055	377	−0.73 (−1.42, −0.02)	0.041
	Hysterectomy and oophorectomy	70	−2.86 (−5.00, −1.07)	0.009	482	−1.20 (−1.87, −0.53)	<0.001
Trunk fat mass	No surgery	1,227	Reference		1,985	Reference	
	Hysterectomy	68	1.76 (−0.04, 3.56)	0.056	377	1.29 (0.23–2.36)	0.017
	Hysterectomy and oophorectomy	70	4.79 (2.08–7.50)	<0.001	482	1.72 (0.78–2.67)	<0.001
Trunk lean mass	No surgery	1,227	Reference		1,985	Reference	
	Hysterectomy	68	−1.70 (−3.46, 0.06)	0.061	377	−1.26 (−2.30, −0.20)	0.016
	Hysterectomy and oophorectomy	70	−4.56 (−7.20, −1.92)	<0.001	482	−1.67 (−2.60, −0.74)	<0.001
Arms fat mass	No surgery	1,227	Reference		1,985	Reference	
	Hysterectomy	68	1.33 (−0.41, 3.03)	0.135	377	0.58 (−0.40, 1.56)	0.242
	Hysterectomy and oophorectomy	70	3.56 (0.75–6.37)	0.013	482	1.13 (0.20–2.14)	0.029
Arms lean mass	No surgery	1,227	Reference		1,985	Reference	
	Hysterectomy	68	−1.11 (−2.76, 0.53)	0.184	377	−0.52 (−1.43, 0.39)	0.259
	Hysterectomy and oophorectomy	70	−3.07 (−5.72, −0.43)	0.023	482	−1.04 (−1.99, −0.09)	0.033
Legs fat mass	No surgery	1,227	Reference		1,985	Reference	
	Hysterectomy	68	0.95 (−0.53, 2.43)	0.208	377	0.14 (−0.54, 0.82)	0.691
	Hysterectomy and oophorectomy	70	1.37 (−0.97, 3.70)	0.252	482	0.87 (0.20, 1.52)	0.011
Legs lean mass	No surgery	1,227	Reference		1,985	Reference	
	Hysterectomy	68	−0.85 (−2.25, 0.54)	0.231	377	−0.16 (−0.81, 0.50)	0.639
	Hysterectomy and oophorectomy	70	−1.07 (−3.28, 1.14)	0.343	482	−0.80 (−1.43, −0.18)	0.012

[a]Median (IQR) time since hysterectomy and oophorectomy, <45 years: 6 years (2–10 years) and ≥45 years: 16 years (7–23 years); median time since hysterectomy, <45 years: 5 years (2–11 years) and ≥45 years: 19 years (12–26 years). Adjusted for age, race, smoking, alcohol use, physical activity, BMI at age 25, parity, oral contraceptive use, and postsurgery ERT use.

Table 3. Multivariable-adjusted mean percent difference and 95% CI for total and regional fat and lean body mass by hysterectomy and oophorectomy status and BMI at DXA scan[a].

		BMI < 25 kg/m^2 (n = 1,177)			BMI ≥ 25 kg/m^2 (n = 2,980)		
DXA measure	Subgroup	n	β (95% CI)	P value	n	β (95% CI)	P value
Total fat mass	No surgery	942	Reference		2,226	Reference	
	Hysterectomy	103	1.00 (−0.19, 2.20)	0.111	339	0.55 (−0.15, 1.26)	0.125
	Hysterectomy and oophorectomy	132	1.89 (0.72–3.04)	0.002	415	0.75 (0.27–1.23)	0.002
Total lean mass	No surgery	942	Reference		2,226	Reference	
	Hysterectomy	103	−0.95 (−2.10, 0.20)	0.105	339	−0.51 (−1.18, 0.16)	0.138
	Hysterectomy and oophorectomy	132	−1.73 (−2.85, −0.60)	0.003	415	−0.70 (−1.15, −0.24)	0.003
Trunk fat mass	No surgery	942	Reference		2,226	Reference	
	Hysterectomy	103	1.32 (−0.17, 2.80)	0.082	339	1.09 (0.20–1.99)	0.018
	Hysterectomy and oophorectomy	132	2.56 (1.14–3.96)	<0.001	415	1.15 (0.51–1.79)	<0.001
Trunk lean mass	No surgery	942	Reference		2,226	Reference	
	Hysterectomy	103	−1.25 (−2.71, 0.19)	0.089	339	−0.32 (−0.73, 0.09)	0.123
	Hysterectomy and oophorectomy	132	−2.45 (−3.82, −1.06)	<0.001	415	−0.40 (−0.68, −0.12)	0.006
Arms fat mass	No surgery	942	Reference		2,226	Reference	
	Hysterectomy	103	1.04 (−0.69, 2.75)	0.237	339	0.31 (−0.62, 1.24)	0.512
	Hysterectomy and oophorectomy	132	1.82 (0.18–3.46)	0.031	415	0.72 (−0.05, 1.48)	0.066
Arms lean mass	No surgery	942	Reference		2,226	Reference	
	Hysterectomy	103	−0.93 (−2.58, 0.73)	0.271	339	−0.24 (−1.12, 0.64)	0.591
	Hysterectomy and oophorectomy	132	−1.65 (−3.25, −0.04)	0.044	415	−0.65 (−1.40, 0.09)	0.085
Legs fat mass	No surgery	942	Reference		2,226	Reference	
	Hysterectomy	103	0.80 (−0.76, 2.35)	0.313	339	−0.20 (−0.99, 0.61)	0.641
	Hysterectomy and oophorectomy	132	1.37 (−0.05, 2.78)	0.059	415	0.21 (−0.46, 0.88)	0.544
Legs lean mass	No surgery	942	Reference		2,226	Reference	
	Hysterectomy	103	−0.83 (−2.35, 0.69)	0.283	339	0.21 (−0.56, 0.97)	0.593
	Hysterectomy and oophorectomy	132	−1.23 (−2.61, 0.15)	0.081	415	−0.19 (−0.83, 0.46)	0.563

[a]Adjusted for age, race, smoking, alcohol use, physical activity, BMI at age 25, parity, oral contraceptive use, and post-surgery ERT use.

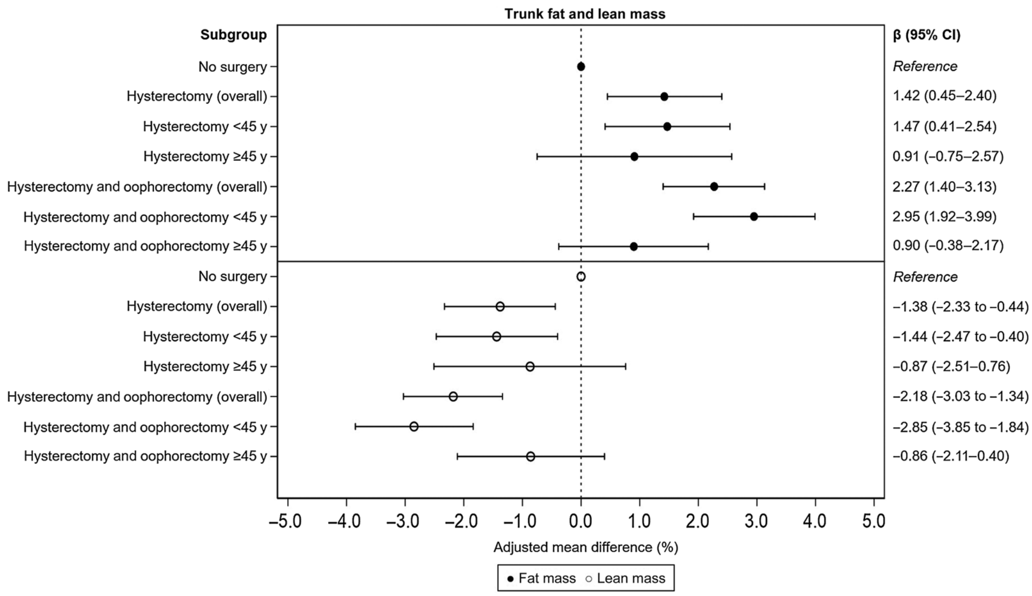

Figure 2.

Multivariable-adjusted mean percent difference and 95% CI for trunk fat and lean mass by hysterectomy and oophorectomy status, overall and by age at surgery. Adjusted for age at interview, race, smoking, alcohol use, education, BMI at age 25, parity, oral contraceptive use, and postsurgery ERT use.

22.1%–42.4%) compared with those who reported no physical activity (54.7%, 95% CI, 49.4%–60.1%; $P < 0.001$). Women who reported moderate physical activity (43.2%, 95% CI, 35.5%–50.8%) also had a lower prevalence of high total fat and low total lean mass compared with women who reported no physical activity (54.7%, 95% CI, 49.4%–60.1%); however, the difference was not statistically significant. Among women with a history of hysterectomy alone, a nonsignificant reduction in the prevalence of high total fat and low total lean mass was observed in women who reported vigorous physical activity (32.0%, 95% CI, 17.7%–46.3%) and women who reported moderate physical activity (39.6%, 95% CI, 31.4%–47.8%) compared with women who reported no physical activity (40.5%, 95% CI, 32.9%–48.1%). A

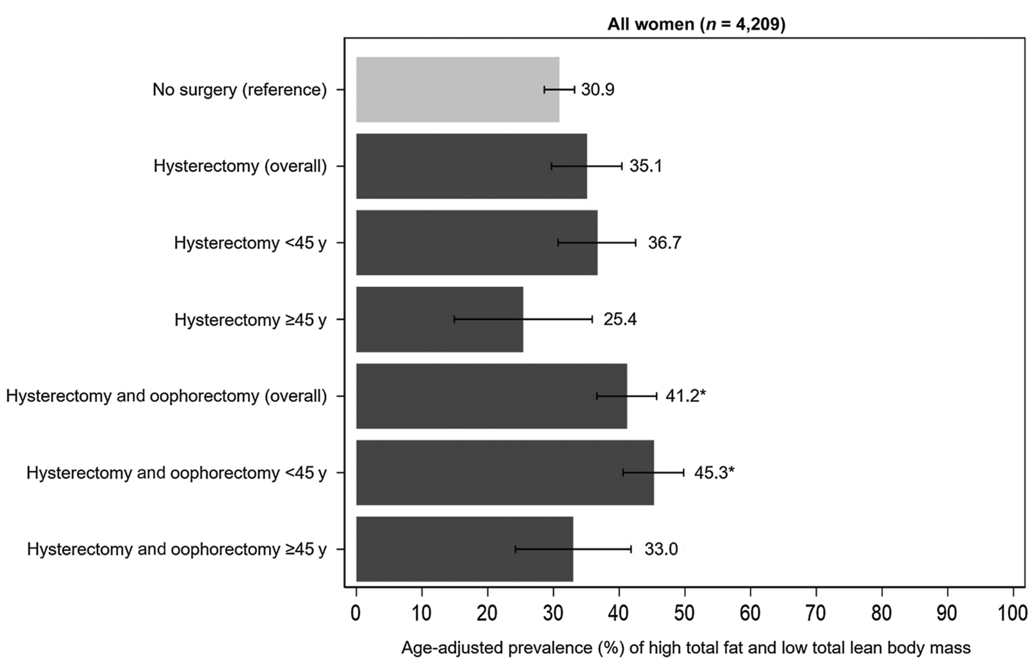

Figure 3.

Age-adjusted prevalence of high total fat and low total lean body mass by hysterectomy and oophorectomy status, overall and by age at surgery. High total fat mass and low total lean body mass defined as total fat mass ≥43.7% (tertile 3) and total lean mass <53.7% (tertile 1). Tertile cut points are based on values among women without a history of hysterectomy and oophorectomy. *, $P < 0.05$ for absolute differences in age-adjusted prevalence (reference group: no surgery).

nonsignificant reduction in the prevalence of high total fat and low total lean mass was observed in women who reported ERT use after oophorectomy (44.4%, 95% CI, 29.5%–49.4%) compared with those who did not (47.8%, 95% CI, 29.5%–49.4%;). There was no difference in the prevalence of high total fat and low total lean mass in women who reported ERT use after hysterectomy (39.2%, 95% CI, 25.0%–53.4%) compared with those who did not (38.4%, 95% CI, 32.5%–44.3%; Supplementary Table S5).

Discussion

To our knowledge, this is the first population-based study to compare DXA measurements of fat and lean body mass in women with a history of hysterectomy with and without oophorectomy. We found that women who had either surgery at a young age had increased total fat mass and decreased total lean mass relative to women with no surgery. However, differences in total fat and lean mass relative to women with intact ovaries and uterus were larger in women with a history of hysterectomy and oophorectomy than women with hysterectomy alone. All body regions (arms, legs, and trunk) were affected for women with hysterectomy and oophorectomy, whereas only the trunk was affected for women with hysterectomy alone. Differences in total and regional fat and lean body mass by oophorectomy status were not limited to women who were overweight or obese but also observed in women with a normal BMI. Furthermore, these differences persisted after excluding women diagnosed with endometriosis and uterine fibroids and those using ERT after surgery. The age-adjusted prevalence of high total fat and low total lean mass was elevated among women with a history of surgery, with 45% of women with hysterectomy and oophorectomy <45 years and 37% of women with hysterectomy <45 years in the top third of total fat mass and the bottom third of total lean mass compared with 30% of women with no surgery.

Similar elevations in total body fat mass and trunk fat mass have been associated with increased cardiovascular disease and breast cancer risk. In the Women's Health Initiative, high trunk fat mass was associated with a 1.9-fold increase in cardiovascular disease risk and a 1.8-fold increase in breast cancer risk in postmenopausal women with a normal BMI (13, 15). Another study, investigating the association between body composition and overall mortality found that women in the lowest quartile of lean body mass had between 1.5- and 2.0-fold increased risk of overall mortality compared with women in other quartiles (35). Declines in lean body mass have also been linked to physical disability and frailty. A prospective study found that women with sarcopenia (severe loss of lean mass) had 1.5- to 2.8 times higher odds of physical disability when considering activities of daily living such as walking, bathing/dressing, and lifting/carrying (36). Another study examining the association between sarcopenia and all-cause mortality found that adults with sarcopenia had higher risk of all-cause mortality compared with adults without sarcopenia, regardless of BMI (37).

The few prior studies that have assessed the association between hysterectomy with and without oophorectomy and adiposity have relied on indirect measures such as BMI (11, 12, 38–40), waist circumference (10, 38), and skinfold thickness (10) and have had small sample sizes. A prospective study found that the annual rate of increase in BMI for women with oophorectomy ($n = 106$) was greater compared with women who underwent natural menopause (0.21 vs. 0.08 kg/m^2, $P = 0.030$), and women with oophorectomy ($n = 97$) had 3 times higher odds (95% CI, 1.48–6.72) of severe obesity (BMI $\geq$ 35 kg/m^2) compared with women with natural menopause (11, 12). Of note, age at oophorectomy in these prior studies was substantially higher than our study (45.7 vs. 40.6 years). For hysterectomy alone, previous studies have found that women with a history of hysterectomy ($n = 76$–236) had slightly higher postsurgery BMI compared with women with no hysterectomy (between 0.13 and 0.96 kg/m^2), and women with hysterectomy had 2 times higher odds (95% CI, 1.04–2.48) of reporting >10-pound weight gain compared with women with no hysterectomy (12, 38, 40). Our results suggest that BMI assessment alone is insufficient as it may mask important differences in fat and lean body mass in women with a normal BMI.

Our findings in younger women may be explained in part by the premature decline in sex hormones after surgery. During natural menopause, production of estrogen and progesterone declines gradually while production of testosterone continues (41, 42). However, oophorectomy before natural menopause causes an abrupt decline in estrogen, progesterone, testosterone, and disruption of the hypothalamic–pituitary–ovarian axis (43, 44). This disturbed hormonal milieu is thought to be a contributor to increased body weight, abdominal fat distribution, and decreased lean mass (45–47). Prior studies have suggested that hysterectomy alone could also result in hormonal changes by disrupting ovarian blood supply (48, 49). Furthermore, changes in fat and muscle tissue in the abdomen could occur during an abdominal hysterectomy, which may explain why the greatest differences in fat and lean mass in our study were observed in the trunk region. Although preclinical models of estrogen supplementation have been shown to counteract these changes (36, 37, 50, 51), our results did not change when women who used postsurgery estrogen were excluded. The Women's Health Initiative substudies reported similar findings. They observed no significant differences in DXA-measured body composition in women randomized to estrogen therapy alone compared with placebo (52). In addition, a recent systematic review showed no significant association between estrogen supplementation and muscle mass retention in postmenopausal women (53).

Our study is subject to some limitations. Due to the cross-sectional design of NHANES, we were unable to assess causality between hysterectomy with and without oophorectomy and body composition. Overweight and obese women are more likely to be diagnosed with certain nonmalignant gynecologic conditions such as uterine fibroids and abnormal menstrual bleeding compared with normal weight women, which may increase their likelihood of gynecologic surgeries. To address this potential bias, we stratified our analyses by BMI at DXA scan and conducted sensitivity analyses excluding women with a diagnosis of endometriosis and uterine fibroids. The relationship between oophorectomy and body composition persisted in BMI-stratified analysis and was stronger in women with a normal BMI at DXA scan, and our results were unchanged after exclusion of women with endometriosis and uterine fibroids. In addition, we did not find a significant difference in BMI at age 25 between women who reported a subsequent surgery compared with women without surgery. Nevertheless, we adjusted for BMI at age 25 in all our multivariable models. Another limitation was that surgery status was self-reported and subject to recall bias. Studies that have investigated agreement of self-reported oophorectomy status indicate that accuracy exceeds 84% irrespective of age at surgery, hysterectomy status, and number of ovaries removed during surgery (54, 55). Last, we cannot be certain that all oophorectomies were opportunistic. We excluded women with a cancer diagnosis from our study population, and our results were unchanged after excluding women who reported a diagnosis of uterine fibroids and endometriosis. Further, prior studies have shown that most bilateral oophorectomies during a nonmalignant hysterectomy in premenopausal women are performed for ovarian cancer prevention (56).

Our study has several strengths. First, NHANES provides a diverse sample of women representative of the U.S. population with standardized protocols for questionnaires, interviewing, and examinations. Second, body composition was objectively measured using DXA scans, a technique that provides accurate, precise, and highly reproducible measures of fat and lean body mass (25, 26). Finally, detailed information on demographic and reproductive factors allowed us to control for multiple important confounders.

In conclusion, our results suggest that hysterectomy with and without oophorectomy at a young age may have adverse effects on total fat and lean body mass, even among women with a normal BMI. The magnitude and extent of changes in fat and lean body mass may be greater in women who undergo hysterectomy with oophorectomy than hysterectomy alone. Prospective studies are needed to further evaluate body composition changes in women undergoing oophorectomy and the assessment of preventive interventions.

Authors' Disclosures

C.E. Joshu reports grants from American Cancer Society during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

P.S. Karia: Conceptualization, data curation, formal analysis, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **C.E. Joshu:** Conceptualization, resources, supervision, methodology, writing–review and editing. **K. Visvanathan:** Conceptualization, resources, supervision, methodology, writing–review and editing.

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