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A prospective study of body size throughout the life-course and the incidence of endometrial cancer among pre- and post-menopausal women

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Abstract

Although adult obesity is known to increase endometrial cancer risk, evidence for childhood obesity is limited. We prospectively examined the association between body fatness throughout life and endometrial cancer risk. 47,289 members of the Nurses' Health Study (NHS) and 105,386 of the Nurses' Health Study II (NHS II) recalled their body fatness at ages 5, 10, and 20 using a pictogram. Childhood and adolescent body fatness were derived as the average at ages 5 and 10, and ages 10 and 20, respectively. We obtained adult weight from concurrent questionnaires. We calculated hazard ratios (HR) of endometrial cancer using Cox proportional hazards models. During follow-up, 757 incident cases of endometrial cancer were diagnosed. Body fatness in childhood, at age 10, in adolescence, and at age 20 were positively associated with endometrial cancer risk (HR for Level 5 versus Level 2 in adolescence: 1.83 (95% CI 1.41-2.37)). After adjusting for most recent BMI, none of the associations persisted. Weight change since age 18 was positively associated with endometrial cancer risk [HR for ≥ 25 kg gain versus stable: 2.54 (95% CI 1.80-3.59)]. Adult BMI was strongly associated with endometrial cancer risk [HR BMI ≥ 35 kg/m² versus BMI ≤ 25 kg/m²: 4.13 (95% CI 3.29-5.16)]. In postmenopausal women, the

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association with BMI was significantly stronger among non-users of hormone therapy. In conclusion, obesity throughout life is positively associated with endometrial cancer risk, with adult obesity one of the strongest risk factors. Maintaining a healthy weight throughout life remains important.

INTRODUCTION

Endometrial cancer is the most common gynecological cancer in the United States, with an estimated 52,630 new cases in 2014.¹ About 40% of endometrial cancer is attributed to overweight and obesity², and thought to occur predominantly via estrogen,^{3,4} but also via insulin-dependent,³ and inflammatory⁵ pathways. While the evidence for an association between adult obesity and endometrial cancer risk is convincing,⁶ the role of early life obesity is unclear.

Childhood obesity could influence development of endometrial cancer in several ways. It may result in earlier menarche,⁷ which increases the risk of endometrial cancer.⁸ Childhood obesity may reduce levels of sex-hormone binding globulin,⁹ which increases levels of non-SHBG-bound estrogen.¹⁰ Conversely, body fatness in childhood is associated with lower levels of insulin growth factor – 1 (IGF-1) in adults,¹¹ which may decrease incidence of adult cancers, including endometrial cancer.

We therefore examined the association between body fatness from early childhood to adulthood, adult weight gain, and endometrial cancer risk, and whether the association between childhood body fatness and endometrial cancer was independent of adult body size. Finally, we stratified the associations by menopausal status, and among postmenopausal women, by postmenopausal hormone therapy (HT) use.

METHODS

Study Population

The study population consists of participants from the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II), two prospective cohort studies that began in 1976 and 1989, respectively. Details of the NHS have been described.¹² Briefly, the NHS included 121,700 female registered nurses, aged between 30 and 55 in 1976, and residing in the United States. The NHS II included 116,430 women, aged between 25 and 42 in 1989, also residing in the United States. Participants provided information on demographics, lifestyle, and medical history at baseline and every two years thereafter via questionnaires. For this study, NHS participants were followed from 1988 - 2010 and NHS II participants from 1989 - 2009, with baseline years defined according to when childhood body fatness was queried. At baseline, we excluded women who were missing information on body fatness at age 5, 10, or 20 (NHS n = 35,503; NHS II n = 3,012), BMI at age 18 (NHS n = 7,410; NHS II n = 1,114), reported a prior hysterectomy (NHS n = 21,934; NHS II n = 5,904), a previous diagnosis of any cancer except non-melanoma skin cancer (NHS n = 5,707; NHS II n = 1,013), and women whose age was unknown (NHS n = 124; NHS II n = 0). Women missing BMI at baseline (NHS n = 849; NHS II n = 402) could enter the study in later follow-up

cycles if BMI was subsequently available. The final population comprised 47,289 participants from NHS and 105,356 participants from NHS II.

Ascertainment of endometrial cancer cases

Participants reported any new diagnosis of endometrial cancer via questionnaires. These were confirmed via medical record review, including diagnosis date, histology, and stage. Case definition was restricted to invasive adenocarcinomas, as these comprise the majority of cases of endometrial cancer. All cases were confirmed in both cohorts.

Assessment of body fatness

NHS and NHS II participants recalled their body fatness at ages 5, 10, and 20 years using a figure developed by Stunkard (Figure 1)¹³, which can be helpful in estimating weight status in the absence of BMI. To reduce the effects of random error, we also evaluated the average of the levels at ages 5 and 10 (i.e. average childhood level) and the average of the levels at ages 10 and 20 (i.e. average adolescent level).

The long-term recall of childhood body fatness was validated during a follow-up of the Third Harvard Growth Study.¹⁴ Using the same figure, interviewed subjects who were aged 71 – 76 years at follow-up, were asked to select the outline that best reflected their body fatness at ages 5, 10, 15, and 20. In women, crude Pearson correlations between recalled body shape and measured BMI at approximately the same ages were 0.60 for age 5, 0.75 for age 10, and 0.66 for age 20. The results did not change appreciably, although attenuated, after adjusting for recent BMI.

Weight and height at age 18 and weight throughout follow-up were obtained via self-report. In a study of 184 NHS participants, the correlation between self-reported and measured weights was high, at 0.96.¹⁵ In another validation study of 118 NHS II participants, recalled weight and height were compared with college or nursing school entrance records.¹⁶ The correlation between reported weight and measured weight was 0.84, and that between self-reported height and measured height was 0.94. Therefore, the validity of self-reports is high in both cohorts.

Recent BMI was calculated as the weight from the questionnaire period prior to case diagnosis in kilograms divided by the square of the height in meters. Weight change since age 18 was calculated as the difference between reported weight from the questionnaire prior to case diagnosis and weight at age 18.

Spearman correlations between recent BMI and body fatness at ages 5, 10, and 20 were 0.15, 0.21, and 0.28 respectively in NHS, and 0.22, 0.32, and 0.40 respectively in NHS II.

Assessment of covariates

The potential risk factors included in our analyses were age, age of menarche, oral contraceptive use, age at last birth/number of pregnancies lasting 6+ months, menopausal status, HT use, smoking, physical activity, hypertension, diabetes, height, and first-degree family history of endometrial cancer and colon or rectal cancer. With the exception of family history of endometrial cancer, which was collected in 1996 for NHS and 2001 for NHS II,

physical activity in adolescence and early adulthood, collected in 2004 for NHS and 1997 for NHS II, and age of menarche and height, collected in 1976 for NHS and 1989 for NHS II, all variables were updated during follow-up.

Statistical Analysis

Participants contributed person-time from baseline until 1 June 2010 for NHS and 1 June 2009 for NHS II or until they were censored due to endometrial or any other cancer (except nonmelanoma skin cancer), a hysterectomy, death, or loss to follow-up.

Body fatness at ages 5 and 10 were categorized as Level 1, 2, 3, 4, and 5-9. Because of the relatively small number of cases in NHS II, we combined the lower two levels of body fatness at age 20. Childhood and adolescent body fatness, which were the average of body fatness at ages 5 and 10, and ages 10 and 20, respectively, were categorized into four groups [Levels 1- 2, 2.5-3, 3.5-4.5, and 5-9].

Most recent body size was assessed using BMI in four groups: 24.9, 25.0-29.9, 30.0-34.9, and 35.0 kg/m². If missing, BMI was imputed by BMI reported in the previous cycle. Weight change was categorized into 8 groups: -2, -2 - < 2 (stable weight), 2 - < 5, 5 - < 10, 10 - < 15, 15 - < 20, 20 - < 25, and 25 kg.

Cox proportional hazards regression was used to estimate multivariable hazard ratios (HR) of endometrial cancer, for body fatness at age 5, 10, and 20, in childhood, adolescence, recent BMI, and weight change, using indicator variables. We performed tests for linear trend by using a single ordinal variable with values 1 through 4 or 5, to represent the levels of body fatness/size at each time point. For weight change, the test for linear trend was performed using an ordinal variable with values 1 through 8.

The basic model was stratified on age (in months), 2-year follow-up cycle, and cohort. We additionally adjusted for smoking, oral contraceptive use, menopausal status and HT use, age at menopause, parity and age at last birth, physical activity during adolescence (average between middle school and high school physical activity), physical activity during early adulthood, recent physical activity, hypertension, diabetes, family history (mother or sister) of endometrial cancer, family history (parent or sibling) of colon or rectal cancer, and height (see Tables 2 - 5 footnotes for categories).

Since menstrual cycle characteristics (age at menarche and menstrual cycle regularity at age 18) and recent BMI are potentially intermediates between childhood body fatness and endometrial cancer, these were assessed in separate models.

To examine whether the association between body fatness/size and endometrial cancer risk was heterogeneous across the cohorts, we created an interaction term between an ordinal variable to represent body fatness/size at each age and cohort, and evaluated the Wald statistic. Although there was heterogeneity in the association between body fatness/size and endometrial cancer risk between NHS and NHS II, the differences were modest and all associations were in the same direction (Table 5), i.e., interactions were quantitative and not qualitative.¹⁷ Therefore, we pooled the data by combining the data from both cohorts and adding an indicator variable to denote cohort.

In secondary analyses in each cohort, we further adjusted for coffee,¹⁸ dairy,¹⁹ acrylamide,²⁰ alcohol intake,²¹ and talc use (NHS only).²² Results from these analyses were not appreciably different from the final models, and were therefore not included in our final tables.

We examined whether the association between body fatness and endometrial cancer risk differed by menopausal status, and among postmenopausal women, by HT use. We created interaction terms between ordinal variables representing body fatness/size at each age and menopausal status (premenopausal/postmenopausal) or HT use (ever/never) and examined the Wald statistic.

RESULTS

In NHS, 590 cases of endometrial cancer were diagnosed during 803,134 person-years of follow-up; of these, 549 were postmenopausal. In NHS II, 167 cases were diagnosed during 1,694,905 person-years, of which 60 were postmenopausal.

Table 1 describes the socio-demographic and reproductive characteristics of the study population. The mean age at baseline for NHS participants was 54 years compared to 34 years for NHS II participants. In NHS, women who reported a body fatness of Level 5 or higher at age 5 or age 10 were slightly younger than those who reported the lowest level of body fatness, although no such difference was observed in NHS II (Table 1). In both cohorts, age at menarche was slightly earlier for those reporting a body fatness of Level 5 or higher at any age.

Body fatness at age 5 was marginally associated with endometrial cancer risk after adjusting for covariates (Table 2). Childhood, age 10, adolescent, and age 20 body fatness, were significantly associated with risk after adjusting for covariates except recent BMI. For example, in adolescence, the HR for Level 5 versus Level 2 was 1.83 (95% CI 1.41-2.37; $p_{\text{trend}} < 0.001$). Higher BMI at age 18 also was strongly associated with an increased risk of endometrial cancer after adjusting for covariates except recent BMI; HR for BMI ≥ 23.0 kg/m² versus BMI < 19.9 kg/m² was 1.64 (95% CI 1.35-1.99; $p_{\text{trend}} < 0.001$). Recent BMI during adulthood was the strongest risk factor: HR for BMI ≥ 35.0 kg/m² versus BMI < 25 kg/m² was 4.13 (95% CI 3.29-5.16; $p_{\text{trend}} < 0.001$).

After adjusting for menstrual cycle characteristics, childhood, age 10, adolescent, and age 20 body fatness were still associated with risk, although attenuated slightly: HR in adolescence for Level 5 versus Level 2 was 1.76 (95% CI 1.35-2.28; $p_{\text{trend}} < 0.001$) (Table 2). After adjusting for recent BMI, none of these associations persisted: HR in adolescence for Level 5 versus Level 2 was 1.03 (95% CI 0.78-1.36; $p_{\text{trend}} = 0.81$).

Weight change since age 18 was positively associated with endometrial cancer risk: the HR for 25+ kg weight gain versus stable weight was 2.54 (95% CI 1.80-3.59; $p_{\text{trend}} < 0.001$) (Table 2). After adjusting for weight at age 18, the association was slightly stronger: compared to women who maintained a stable weight, HR for women who gained 25+ kg was 2.71 (95% CI 1.92-3.82; $p_{\text{trend}} < 0.001$). Women who at age 18 had a BMI ≥ 21 kg/m² were at greater risk ($p_{\text{interaction}} < 0.001$); HR = 2.86 (95% CI 1.80-4.54; $p_{\text{trend}} < 0.001$),

versus 2.13 (95% CI 1.26-3.61; $p_{\text{trend}} < 0.001$) for BMI $< 21 \text{ kg/m}^2$. We also examined the association between weight change since age 18 and endometrial cancer risk, adjusting for recent weight instead of weight at age 18. After adjusting for recent weight, the association between weight change since age 18 and endometrial cancer was attenuated and no longer significant (HR for 25+ kg weight gain versus stable weight was 0.78 (95% CI 0.52-1.16; $p_{\text{trend}} = 0.23$).

We also stratified by menopausal status (Table 3). In postmenopausal women, body fatness was associated with endometrial cancer risk at age 10, during adolescence, and at age 20. In adolescence, the HR for Level 5 versus Level 2 was 1.56 (95% CI 1.15-2.12; $p_{\text{trend}} = 0.002$). Recent BMI was also associated with endometrial cancer risk. The associations were stronger in premenopausal women: body fatness was associated with endometrial cancer risk at every age, although the test for interaction was significant only for adolescence, age 20, and recent BMI. In adolescence, the HR for Level 5 versus Level 2 was 3.03 (95% CI 1.71-5.37; $p_{\text{trend}} = 0.002$). However, the associations attenuated and became non-significant after controlling for recent BMI.

Finally, we stratified by HT use among postmenopausal women (Table 4). With the exception of body fatness at age 5 and in childhood, the association of endometrial cancer with body fatness varied by HT use (all $p_{\text{interaction}} < 0.05$). Early life body fatness was unrelated to endometrial cancer among women who reported using HT after menopause. However, recent BMI was still strongly associated with endometrial cancer risk. Among HT non-users, body fatness at age 10, during adolescence, and at age 20 were positively associated with endometrial cancer risk, although non-significant after adjusting for recent BMI. Recent BMI was very strongly associated with endometrial cancer risk, with postmenopausal women with BMI $\geq 35 \text{ kg/m}^2$ at highest risk: adjusted HR versus BMI $< 25 \text{ kg/m}^2$, was 9.31 (95% CI 5.64-15.35; $p_{\text{trend}} < 0.001$).

DISCUSSION

In our study, recent body size, as expected, was strongly associated with endometrial cancer risk, especially among obese women who have never used HT. Weight gain since age 18 years was strongly associated with risk, particularly for women who were heavier at age 18. Early life body fatness was positively associated with endometrial cancer risk, although the association was mediated by adult BMI. Finally, the association between early life body fatness and endometrial cancer risk was stronger in premenopausal than postmenopausal women, although it no longer persisted after adjusting for recent BMI.

Consistent with a number of studies,^{23, 24} we observed that recent obesity was strongly related to endometrial cancer risk. In premenopausal women, obesity is associated with an increased number of anovulatory cycles,²⁵ which is associated with an increased risk of endometrial cancer.^{3, 23} In postmenopausal women, obesity may influence endometrial cancer risk by the increased conversion of androstendione into estrone,²⁶ a biologically active estrogen that can be converted to estradiol. In both pre- and postmenopausal women, obesity may also increase risk via an increase in IGF-1 levels.²⁷

Our study confirms the findings from a previous case-control study in Hawaii²⁸ and a prospective cohort study in the United Kingdom,²⁹ that the association between body size during adolescence and early adulthood may be mediated by adult BMI. In a case-control study in China,³⁰ Xu et al reported an increased risk of endometrial cancer for women who were heavier than their peers during adolescence, although this was limited to women with a BMI of ≥ 25 kg/m², and likely not independent of recent BMI. In a prospective cohort study of US teenagers,³¹ Blitzer et al reported a positive association of teen-age body size with endometrial cancer risk; however, current body size was not taken into account. To our knowledge, body fatness before age 10 had not been previously examined.

Consistent with a number of studies,^{24, 30, 32, 33} but not all,³⁴ weight change since age 18 was positively associated with endometrial cancer risk. A larger body size is correlated with lower levels of SHBG⁹ and consequently an increase in non-SHBG bound estrogen,¹⁰ which can increase the risk of endometrial cancer³. Weight loss is associated with a return to normal SHBG levels,³⁵ suggesting that the converse is true for weight gain. The stronger association between weight gain and endometrial cancer risk among women who were heavier at age 18 likely reflects the positive association between body fatness and endometrial cancer risk. The association was not significant after controlling for current weight, suggesting that this association is mediated by current weight.

We also observed (before adjusting for recent BMI) that the association between early life body fatness and endometrial cancer risk was stronger in premenopausal than postmenopausal women, consistent with the findings of Xu et al.³⁰ Early life obesity is associated with hyperandrogenism,^{36, 37} which is believed to be a risk factor for endometrial cancer among relatively younger women,³⁸ although this has not been observed in some studies.^{39, 40} Further, younger women may more accurately recall their body fatness, and thus a lesser degree of non-differential exposure misclassification. Lastly, the correlation between early life body fatness and adult BMI was stronger in the younger NHS II population, likely due partly to a birth cohort effect,⁴¹ their younger age, and the shorter time between the two measurements.

Consistent with our findings, other studies have also reported that the association between body size and endometrial cancer risk is modified by HT use.⁴²⁻⁴⁵ Serum estradiol and estrone levels among HT users compared with non-users are around 3 to 4 times higher,⁴⁶ compared with about 1.4 to 1.6 times elevated levels for obese women relative to normal weight women.⁴⁷ Thus, among women who use HT, the contribution of estrogen levels to the overall risk of endometrial cancer by obesity may not be as apparent.⁶ Our observed interaction between body fatness in early life and HT use may simply reflect the positive correlation between body size in early life and adulthood.

Limitations of our study include the use of remote recall of early life body fatness, which may result in misclassification. However, since body weight was recalled prior to diagnosis of endometrial cancer, any misclassification would be non-differential. Significant independent associations⁴⁸⁻⁵⁰ observed with this measure give credence to its validity.

Strengths include the prospective analysis of life-course body size (and the first to examine body fatness prior to age 10) and endometrial cancer risk. Further, we have measured and adjusted for several potential confounders, although the possibility of unmeasured or residual confounding cannot be eliminated.

In conclusion, obesity throughout life is positively associated with endometrial cancer risk. Although adult obesity appears to be most strongly associated with endometrial cancer risk, maintaining a healthy weight from childhood remains important, as early life obesity is strongly correlated with adult obesity, which has many adverse health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Impact Statement

Adult body size is a well-established risk factor for endometrial cancer, the most common gynecological malignancy. However, data are limited on the association with childhood obesity. In one of the first prospective studies on the subject, we examined the association between body size throughout the life-course and endometrial cancer risk among participants of the Nurses' Health Studies. Body size throughout life was positively associated with endometrial cancer risk, most strongly in adulthood.

Which diagram best depicts your outline at each age?

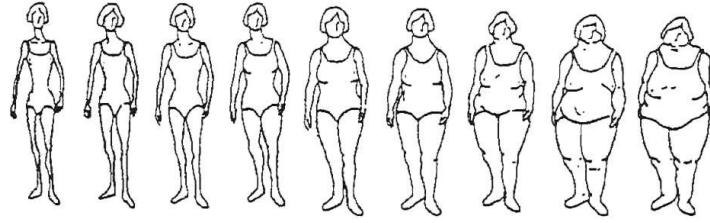


Figure 1.
Nine-level figure for assessing body fatness at ages 5, 10, and 20 years

Table 1

Cumulative age-standardized characteristics of NHS (1998-2010) and NHS II (1989-2009) participants by body fatness at ages 5, 10, and 20.

| | Nurses' Health Study | | | | | |
|--|----------------------|-------------------|-------------------|-------------------|------------------|-------------------|
| | Age 5 | | Age 10 | | Age 20 | |
| | Level 1 (n=19187) | Level 5+ (n=3690) | Level 1 (n=14447) | Level 5+ (n=5701) | Level 1 (n=5313) | Level 5+ (n=4018) |
| Age ¹ | 63.5 (9.2) | 62.4 (9.2) | 63.7 (9.2) | 61.6 (9.1) | 64.0 (9.1) | 62.8 (9.2) |
| Age at menarche, years | 12.7 (1.4) | 12.3 (1.4) | 12.8 (1.4) | 12.2 (1.4) | 12.9 (1.4) | 12.3 (1.4) |
| Regular menstrual cycles at age 18, % | 77.9 | 77.0 | 77.4 | 76.9 | 76.2 | 75.5 |
| BMI at age 18, mean, kg/m ² | 20.3 (2.4) | 24.1 (3.8) | 19.8 (2.1) | 24.1 (3.7) | 18.9 (1.8) | 26.0 (3.8) |
| Adult body mass index, kg/m ² | 25.5 (4.7) | 28.1 (6.4) | 25.0 (4.4) | 28.2 (6.3) | 24.5 (3.9) | 29.6 (7.1) |
| Parous, % | 93.2 | 92.6 | 93.0 | 92.6 | 92.0 | 91.4 |
| Number of children ² | 3.2 (1.5) | 3.0 (1.5) | 3.2 (1.5) | 3.0 (1.4) | 3.2 (1.5) | 3.0 (1.4) |
| Age at last birth ² | 31.6 (4.5) | 31.2 (4.3) | 31.6 (4.5) | 31.1 (4.3) | 31.8 (4.5) | 31.4 (4.4) |
| Postmenopausal, % | 86.3 | 86.2 | 86.3 | 86.0 | 86.5 | 86.0 |
| Age at menopause ³ | 50.2 (3.6) | 50.3 (3.9) | 50.3 (3.5) | 50.3 (3.9) | 50.1 (3.6) | 50.4 (3.8) |
| Ever used HT therapy ³ , % | 58.8 | 57.2 | 59.8 | 58.7 | 59.7 | 55.6 |
| Ever used oral contraceptives, % | 47.9 | 48.9 | 48.2 | 50.4 | 46.9 | 48.2 |
| Ever a smoker, % | 54.7 | 62.4 | 53.7 | 63.2 | 54.3 | 62.5 |
| History of hypertension, % | 34.8 | 36.9 | 33.8 | 37.5 | 33.5 | 39.8 |
| History of diabetes, % | 6.1 | 7.5 | 5.6 | 7.8 | 5.7 | 9.8 |
| Family history of endometrial cancer, % | 3.4 | 2.6 | 3.3 | 2.8 | 3.2 | 2.7 |
| Family history of colorectal cancer, % | 7.9 | 7.6 | 8.1 | 7.6 | 8.5 | 7.7 |
| Adolescent physical activity, METS/week | 43.2 (34.1) | 38.7 (31.1) | 43.7 (34.7) | 37.9 (30.2) | 43.7 (35.0) | 37.8 (30.2) |
| Early adulthood physical activity, METS/week | 31.4 (30.7) | 29.5 (28.6) | 31.5 (31.0) | 28.7 (27.8) | 31.5 (31.8) | 28.1 (27.9) |
| Current physical activity, METS/week | 18.1 (23.8) | 17.8 (23.0) | 18.0 (23.1) | 18.2 (22.9) | 18.0 (23.3) | 16.8 (21.5) |
| Height, in | 64.5 (2.4) | 64.7 (2.5) | 64.5 (2.5) | 64.6 (2.4) | 64.5 (2.6) | 64.7 (2.4) |

| | Nurses' Health Study II | | | | | |
|------------------|-------------------------|-------------------|-------------------|--------------------|------------------|--------------------|
| | Age 5 | | Age 10 | | Age 20 | |
| | Level 1 (n=25809) | Level 5+ (n=7268) | Level 1 (n=19614) | Level 5+ (n=12786) | Level 1 (n=4661) | Level 5+ (n=11493) |
| Age ¹ | 42.2 (7.4) | 42.4 (7.3) | 42.3 (7.4) | 42.4 (7.3) | 43.5 (7.2) | 41.9 (7.3) |

Nurses' Health Study II

| | Age 5 | | Age 10 | | Age 20 | |
|--|-------------------|-------------------|-------------------|--------------------|------------------|--------------------|
| | Level 1 (n=25809) | Level 5+ (n=7268) | Level 1 (n=19614) | Level 5+ (n=12786) | Level 1 (n=4661) | Level 5+ (n=11493) |
| Birth weight >= 8.5 lb, % | 8.2 | 15.9 | 8.5 | 14.0 | 8.8 | 14.1 |
| Age at menarche, years | 12.7 (1.5) | 12.0 (1.4) | 12.8 (1.5) | 12.0 (1.4) | 12.8 (1.5) | 12.1 (1.5) |
| Regular menstrual cycles at age 18, % | 76.9 | 74.6 | 76.9 | 75.0 | 72.7 | 72.8 |
| BMI at age 18, mean, kg/m ² | 20.0 (2.6) | 24.3 (4.9) | 19.3 (2.1) | 24.3 (4.7) | 18.3 (1.7) | 26.6 (4.6) |
| Adult body mass index, kg/m ² | 24.5 (5.1) | 29.3 (7.6) | 23.5 (4.2) | 29.4 (7.6) | 22.5 (3.5) | 31.8 (8.5) |
| Parous, % | 72.1 | 65.6 | 72.3 | 67.0 | 71.6 | 57.9 |
| Number of children ² | 2.2 (0.9) | 2.2 (0.9) | 2.2 (0.9) | 2.2 (0.9) | 2.2 (0.9) | 2.1 (0.9) |
| Age at last birth ² | 30.6 (4.7) | 30.6 (4.8) | 30.7 (4.7) | 30.6 (4.7) | 30.6 (4.7) | 31.0 (5.0) |
| Ever used oral contraceptives, % | 86.1 | 82.9 | 86.3 | 83.1 | 85.0 | 79.8 |
| Postmenopausal, % | 14.0 | 14.2 | 13.9 | 14.1 | 14.5 | 14.1 |
| Age at menopause ³ | 48.1 (4.6) | 47.8 (5.0) | 48.4 (4.6) | 48.1 (5.0) | 48.0 (4.4) | 48.1(5.2) |
| Ever used HT therapy ³ , % | 22.5 | 23.7 | 22.3 | 24.0 | 23.7 | 23.8 |
| Ever a smoker, % | 34.0 | 41.4 | 33.7 | 41.0 | 36.2 | 39.7 |
| History of hypertension, % | 10.1 | 15.1 | 8.8 | 15.4 | 8.1 | 19.0 |
| History of diabetes, % | 1.7 | 3.1 | 1.4 | 3.4 | 1.0 | 5.2 |
| Family history of endometrial cancer, % | 2.3 | 2.7 | 2.4 | 2.5 | 2.5 | 2.6 |
| Family history of colorectal cancer, % | 4.3 | 4.4 | 4.3 | 4.5 | 4.5 | 4.4 |
| Adolescent physical activity, METS/week | 53.8 (36.8) | 45.6 (33.5) | 54.8 (37.0) | 43.7 (32.4) | 53.9 (38.2) | 44.7 (32.9) |
| Early adulthood physical activity, METS/week | 43.7 (33.8) | 40.9 (33.1) | 44.1 (34.0) | 40.1 (32.5) | 43.9 (35.4) | 37.6 (30.7) |
| Current physical activity, METS/week | 22.2 (30.5) | 21.4 (30.2) | 22.4 (31.0) | 20.8 (28.4) | 23.2 (33.1) | 19.6 (27.3) |
| Height, in | 64.8 (2.6) | 65.0 (2.6) | 64.9 (2.7) | 65.0 (2.6) | 64.8 (2.8) | 65.1 (2.67) |

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

¹Value is not age-adjusted

²Among parous women only.

³Among post-menopausal women only

Table 2

Age- and multivariable adjusted hazard ratios and 95% confidence intervals for endometrial cancer by life-course body fatness among NHS (1988-2010) and NHS II (1989-2009) participants

| | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate adjusted HR ³ + Menstrual cycle characteristics ⁴ (95% CI) | Multivariate adjusted HR ³ + BMI ^{5,6} (95% CI) |
|--|------------------------|-----------------|--|---|---|
| Body fatness^f at age 5, Level | | | | | |
| 1 | 264 / 731,584 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2 | 193 / 731,679 | 1.10 | 1.10 (0.91-1.33) | 1.09 (0.90-1.32) | 1.09 (0.90-1.32) |
| 3 | 136 / 553,864 | 1.02 | 1.02 (0.83-1.26) | 1.00 (0.81-1.23) | 0.91 (0.73-1.11) |
| 4 | 95 / 304,037 | 1.21 | 1.19 (0.94-1.51) | 1.16 (0.91-1.47) | 0.95 (0.74-1.21) |
| 5+ | 69 / 176,878 | 1.30 | 1.27 (0.97-1.66) | 1.23 (0.94-1.61) | 0.92 (0.70-1.21) |
| P trend | | 0.05 | 0.08 | 0.15 | 0.30 |
| Body fatness^f at age 10, Level | | | | | |
| 1 | 190 / 554,482 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2 | 196 / 736,442 | 1.07 | 1.09 (0.89-1.33) | 1.07 (0.87-1.31) | 1.04 (0.85-1.27) |
| 3 | 147 / 532,689 | 1.17 | 1.18 (0.95-1.47) | 1.14 (0.92-1.42) | 1.00 (0.80-1.25) |
| 4 | 100 / 374,512 | 1.12 | 1.10 (0.86-1.41) | 1.06 (0.83-1.36) | 0.83 (0.64-1.06) |
| 5+ | 124 / 299,917 | 1.58 | 1.54 (1.22-1.94) | 1.47 (1.17-1.86) | 1.05 (0.82-1.33) |
| P trend | | <0.001 | 0.001 | 0.01 | 0.65 |
| Body fatness^f at age 20, Level | | | | | |
| 1,2 | 270 / 839,815 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3 | 222 / 915,989 | 0.95 | 0.95 (0.79-1.13) | 0.93 (0.77-1.11) | 0.82 (0.68-0.98) |
| 4 | 158 / 492,248 | 1.31 | 1.29 (1.05-1.57) | 1.24 (1.02-1.52) | 0.94 (0.77-1.16) |
| 5+ | 107 / 249,990 | 1.75 | 1.65 (1.31-2.07) | 1.61 (1.28-2.02) | 0.93 (0.73-1.20) |
| P trend | | <0.001 | <0.001 | <0.001 | 0.62 |
| Average childhood body fatness (ages 5 – 10)^g, Level | | | | | |
| 1-2 | 381 / 1,263,067 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2.5-3 | 168 / 589,824 | 1.17 | 1.17 (0.97-1.41) | 1.14 (0.95-1.37) | 1.03 (0.85-1.24) |
| 3.5-4.5 | 138 / 483,640 | 1.17 | 1.14 (0.94-1.39) | 1.11 (0.91-1.35) | 0.89 (0.72-1.08) |

| | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate adjusted HR ³ + Menstrual cycle characteristics ⁴ (95% CI) | Multivariate adjusted HR ³ + recent BMI ^{5,6} (95% CI) |
|--|------------------------|-----------------|--|---|--|
| 5+ | 70 / 161,512 | 1.47 | 1.43 (1.11-1.85) | 1.39 (1.07-1.80) | 0.97 (0.75-1.27) |
| P trend | | 0.003 | 0.01 | 0.02 | 0.44 |
| Average adolescent body fatness (ages 10 – 20)², Level | | | | | |
| 1-2 | 261 / 816,097 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2.5-3 | 208 / 831,429 | 1.03 | 1.03 (0.86-1.24) | 1.01 (0.84-1.21) | 0.92 (0.76-1.11) |
| 3.5-4.5 | 211 / 697,746 | 1.28 | 1.27 (1.05-1.52) | 1.22 (1.01-1.47) | 0.93 (0.77-1.13) |
| 5+ | 77 / 152,771 | 1.92 | 1.83 (1.41-2.37) | 1.76 (1.35-2.28) | 1.03 (0.78-1.36) |
| P trend | | <0.001 | <0.001 | <0.001 | 0.81 |
| BMI at age 18, kg/m² | | | | | |
| 19.9 | 216 / 931,989 | 1.00 | 1.00 | 1.00 | 1.00 |
| 20.0-21.4 | 181 / 646,539 | 1.07 | 1.10 (0.90-1.34) | 1.08 (0.88-1.31) | 0.94 (0.77-1.15) |
| 21.5-22.9 | 135 / 405,503 | 1.17 | 1.19 (0.95-1.48) | 1.15 (0.93-1.44) | 0.89 (0.71-1.11) |
| 23.0 | 225 / 514,012 | 1.70 | 1.64 (1.35-1.99) | 1.58 (1.30-1.92) | 0.91 (0.74-1.13) |
| P trend | | <0.001 | <0.001 | <0.001 | 0.34 |
| Recent BMI, kg/m² | | | | | |
| 24.9 | 242 / 1,323,670 | 1.00 | 1.00 | 1.00 | N/A ⁷ |
| 25.0-29.9 | 202 / 679,660 | 1.22 | 1.23 (1.01-1.49) | 1.22 (1.00-1.47) | |
| 30.0-34.9 | 150 / 295,189 | 2.14 | 2.12 (1.71-2.63) | 2.08 (1.68-2.58) | |
| 35.0 | 163 / 199,524 | 4.34 | 4.13 (3.29-5.16) | 4.05 (3.24-5.07) | |
| P trend | | <0.001 | <0.001 | <0.001 | |
| Weight change since age 18, kg | | | | | |
| Loss (- 2) | 32 / 196,640 | 0.76 | 0.76 (0.48-1.21) | 0.76 (0.48-1.21) | 0.60 (0.37-0.95) |
| Stable (-2 to +2) | 41 / 225,427 | 1.00 | 1.00 | 1.00 | 1.00 |
| Gain (+2 - <5) | 55 / 305,761 | 1.11 | 1.10 (0.73-1.65) | 1.10 (0.73-1.65) | 1.15 (0.76-1.73) |
| (+5 - <10) | 104 / 482,117 | 1.16 | 1.16 (0.81-1.66) | 1.16 (0.81-1.67) | 1.26 (0.87-1.81) |
| (+10 - <15) | 98 / 404,216 | 1.13 | 1.11 (0.77-1.60) | 1.11 (0.77-1.60) | 1.22 (0.85-1.77) |
| (+15 - <20) | 100 / 290,139 | 1.45 | 1.40 (0.97-2.02) | 1.40 (0.97-2.02) | 1.54 (1.07-2.23) |
| (+20 - <25) | 75 / 207,044 | 1.48 | 1.43 (0.97-2.10) | 1.42 (0.96-2.09) | 1.57 (1.06-2.31) |
| (+ 25) | 252 / 386,699 | 2.83 | 2.54 (1.80-3.55) | 2.52 (1.78-3.55) | 2.71 (1.92-3.82) |

| No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate adjusted HR ³ + Menstrual cycle characteristics ⁴ (95% CI) | Multivariate adjusted HR ³ + recent BMI ^{5,6} (95% CI) |
|------------------------|-----------------|--|---|--|
| P trend | <0.001 | <0.001 | <0.001 | <0.001 |

¹ Participants were asked to recall their body fitness at ages 5, 10, and 20, using a nine-level drawing (Figure 1), where Level 1 corresponds to the leanest and Level 9 the most overweight.

² Average childhood and adolescent body fitness were the average of the levels at ages 5 and 10, and ages 10 and 20 respectively.

³ Adjusted for smoking history [never, past, current], oral contraceptive use [never, <3 years, 3-5 years, > 5years], postmenopausal hormone use [premenopausal (reference), post-menopausal – never; postmenopausal – past; post-menopausal current – estrogen only; postmenopausal current – estrogen & progesterone / other], age at menopause [premenopausal/unknown, <45 years, 45-<47 years, 47 - <49 years, 49- <51 years, 51- <53 years, 53+ years], family history of colon/rectal cancer, family history of endometrial cancer, height (inches; continuous), parity and age at last birth[1-2 & <30 yrs, 1-2 & 30 yrs, 3-4 & < 30 yrs, 3-4 & 30 yrs, 5 children], physical activity [adolescent & age 20 models: <21, 21-<36, 36-<53, 54-<81, 81+ METS/week; weight change /recent BMI model: <3, 3-<9, 9-<18, 18-<27, 27+ METS/week]

⁴ Menstrual cycle characteristics: age of menarche [11, 12, 13, 14 years], menstrual cycle regularity at age 18 [regular, irregular/no periods]

⁵ BMI: body mass index

⁶ Weight change model adjusted for weight at age 18, not recent BMI

⁷ Recent BMI models not adjusted for recent BMI

Table 3

Age- and multivariable-adjusted hazard ratios and 95% confidence intervals for endometrial cancer by life-course body fatness, stratified by menopausal status

| | | POSTMENOPAUSAL WOMEN | | | | PREMENOPAUSAL WOMEN | | | |
|--|------------------------|----------------------|--|--|------------------------|---------------------|--|--|--|
| | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | |
| Body fatness^J at age 5, Level | | | | | | | | | |
| 1 | 233 / 331,397 | 1.00 | 1.00 | 1.00 | 28 / 364,247 | 1.00 | 1.00 | 1.00 | |
| 2 | 146 / 216,055 | 1.05 | 1.05 (0.85-1.29) | 1.03 (0.83-1.27) | 43 / 476,598 | 1.41 | 1.43 (0.88-2.32) | 1.42 (0.87-2.30) | |
| 3 | 103 / 167,183 | 0.98 | 0.98 (0.78-1.24) | 0.89 (0.70-1.13) | 31 / 356,807 | 1.25 | 1.14 (0.67-1.94) | 0.95 (0.55-1.63) | |
| 4 | 76 / 99,000 | 1.21 | 1.20 (0.92-1.55) | 0.99 (0.76-1.29) | 16 / 188,861 | 1.16 | 1.03 (0.54-1.94) | 0.73 (0.38-1.38) | |
| 5+ | 51 / 67,464 | 1.16 | 1.15 (0.84-1.56) | 0.89 (0.65-1.21) | 18 / 99,916 | 2.50 | 2.21 (1.20-4.07) | 1.31 (0.70-2.48) | |
| <i>P_{trend}</i> | | 0.21 | 0.25 | 0.40 | | 0.04 | 0.15 | 0.69 | |
| <i>P_{interaction}</i> | | | | | | | 0.19 | | |
| Body fatness^J at age 10, Level | | | | | | | | | |
| 1 | 167 / 252,273 | 1.00 | 1.00 | 1.00 | 21 / 275,430 | 1.00 | 1.00 | 1.00 | |
| 2 | 160 / 238,483 | 1.08 | 1.09 (0.88-1.36) | 1.04 (0.83-1.30) | 32 / 459,346 | 1.07 | 1.11 (0.63-1.95) | 1.04 (0.59-1.84) | |
| 3 | 106 / 164,862 | 1.06 | 1.08 (0.84-1.38) | 0.93 (0.72-1.19) | 37 / 339,548 | 1.61 | 1.53 (0.88-2.67) | 1.18 (0.67-2.07) | |
| 4 | 78 / 119,026 | 1.10 | 1.09 (0.83-1.43) | 0.86 (0.65-1.13) | 21 / 235,247 | 1.26 | 1.06 (0.56-1.99) | 0.69 (0.36-1.31) | |
| 5+ | 98 / 106,454 | 1.56 | 1.53 (1.19-1.97) | 1.12 (0.86-1.46) | 25 / 176,856 | 1.97 | 1.77 (0.97-3.22) | 0.90 (0.47-1.70) | |
| <i>P_{trend}</i> | | 0.004 | 0.01 | 0.98 | | 0.02 | 0.10 | 0.38 | |
| <i>P_{interaction}</i> | | | | | | | 0.42 | | |
| Body fatness^J at age 20, Level | | | | | | | | | |
| 1,2 | 227 / 347,818 | 1.00 | 1.00 | 1.00 | 36 / 449,844 | 1.00 | 1.00 | 1.00 | |
| 3 | 189 / 299,323 | 1.02 | 1.02 (0.84-1.24) | 0.90 (0.74-1.10) | 31 / 568,858 | 0.73 | 0.71 (0.44-1.16) | 0.59 (0.36-0.97) | |
| 4 | 119 / 155,345 | 1.26 | 1.23 (0.98-1.54) | 0.94 (0.74-1.18) | 38 / 311,023 | 1.72 | 1.60 (0.99-2.57) | 0.99 (0.60-1.65) | |
| 5+ | 74 / 78,613 | 1.54 | 1.46 (1.12-1.91) | 0.92 (0.69-1.22) | 31 / 156,705 | 3.04 | 2.36 (1.40-3.97) | 1.02 (0.56-1.87) | |
| <i>P_{trend}</i> | | <0.001 | 0.004 | 0.51 | | <0.001 | <0.001 | 0.65 | |

| POSTMENOPAUSAL WOMEN | | | | | | | PREMENOPAUSAL WOMEN | | | | | | |
|--|------------------------|-----------------|--|--|------------------------|-----------------|--|--|------------------|--------|------------------|------------------|------------------|
| | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | | | | | |
| <i>P</i> _{interaction} ⁶ | | | | | | | | | 0.01 | | | | |
| Average childhood body fatness (ages 5 – 10)², Level | | | | | | | | | | | | | |
| 1,1,5,2 | 324 / 484,396 | 1.00 | 1.00 | 1.00 | 51 / 714,738 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2,5,3 | 127 / 181,803 | 1.11 | 1.12 (0.91-1.37) | 1.00 (0.81-1.23) | 39 / 376,434 | 1.47 | 1.36 (0.88-2.09) | 1.13 (0.73-1.75) | 1.36 (0.88-2.09) | 1.47 | 1.36 (0.88-2.09) | 1.13 (0.73-1.75) | 1.13 (0.73-1.75) |
| 3,5,4,4,5 | 106 / 152,859 | 1.14 | 1.12 (0.90-1.40) | 0.91 (0.73-1.14) | 28 / 304,397 | 1.28 | 1.09 (0.68-1.76) | 0.71 (0.43-1.17) | 1.09 (0.68-1.76) | 1.28 | 1.09 (0.68-1.76) | 0.71 (0.43-1.17) | 0.71 (0.43-1.17) |
| 5+ | 52 / 62,041 | 1.33 | 1.30 (0.97-1.75) | 0.96 (0.71-1.30) | 18 / 90,859 | 2.68 | 2.31 (1.33-4.02) | 1.22 (0.67-2.21) | 2.31 (1.33-4.02) | 2.68 | 2.31 (1.33-4.02) | 1.22 (0.67-2.21) | 1.22 (0.67-2.21) |
| <i>P</i> _{trend} | | 0.04 | 0.06 | 0.52 | | 0.004 | 0.03 | 0.78 | 0.03 | 0.004 | 0.03 | 0.78 | 0.78 |
| <i>P</i> _{interaction} ⁶ | | | | | | | | | 0.10 | | | | |
| Average adolescent body fatness (ages 10 – 20)², Level | | | | | | | | | | | | | |
| 1,1,5,2 | 225 / 344,630 | 1.00 | 1.00 | 1.00 | 32 / 431,026 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2,5,3 | 166 / 264,517 | 1.02 | 1.02 (0.84-1.25) | 0.92 (0.75-1.13) | 37 / 523,422 | 1.08 | 1.05 (0.65-1.69) | 0.89 (0.55-1.45) | 1.05 (0.65-1.69) | 1.08 | 1.05 (0.65-1.69) | 0.89 (0.55-1.45) | 0.89 (0.55-1.45) |
| 3,5,4,4,5 | 165 / 218,560 | 1.27 | 1.26 (1.02-1.54) | 0.98 (0.80-1.21) | 44 / 441,532 | 1.45 | 1.30 (0.81-2.08) | 0.80 (0.48-1.33) | 1.30 (0.81-2.08) | 1.45 | 1.30 (0.81-2.08) | 0.80 (0.48-1.33) | 0.80 (0.48-1.33) |
| 5+ | 53 / 53,391 | 1.63 | 1.56 (1.15-2.12) | 0.98 (0.71-1.35) | 23 / 90,448 | 3.81 | 3.03 (1.71-5.37) | 1.22 (0.63-2.36) | 3.03 (1.71-5.37) | 3.81 | 3.03 (1.71-5.37) | 1.22 (0.63-2.36) | 1.22 (0.63-2.36) |
| <i>P</i> _{trend} | | <0.001 | 0.002 | 0.86 | | <0.001 | 0.002 | 0.98 | 0.002 | <0.001 | 0.002 | 0.98 | 0.98 |
| <i>P</i> _{interaction} ⁶ | | | | | | | | | 0.05 | | | | |
| Recent BMI, kg/m² | | | | | | | | | | | | | |
| 24.9 | 196 / 406,469 | 1.00 | 1.00 | N/A ⁵ | 41 / 853,801 | 1.00 | 1.00 | N/A ⁵ | 1.00 | 1.00 | 1.00 | N/A ⁵ | N/A ⁵ |
| 25.0-29.9 | 171 / 283,070 | 1.22 | 1.23 (1.00-1.52) | | 29 / 361,032 | 1.26 | 1.28 (0.78-2.08) | | 1.28 (0.78-2.08) | 1.26 | 1.28 (0.78-2.08) | | |
| 30.0-34.9 | 123 / 122,265 | 2.12 | 2.10 (1.65-2.67) | | 25 / 155,642 | 2.47 | 2.48 (1.47-4.17) | | 2.48 (1.47-4.17) | 2.47 | 2.48 (1.47-4.17) | | |
| 35.0 | 119 / 69,295 | 4.12 | 3.97 (3.06-5.14) | | 41 / 115,954 | 5.22 | 4.43 (2.68-7.34) | | 4.43 (2.68-7.34) | 5.22 | 4.43 (2.68-7.34) | | |
| <i>P</i> _{trend} | | <0.001 | <0.001 | | | <0.001 | <0.001 | | <0.001 | <0.001 | <0.001 | | |
| <i>P</i> _{interaction} ⁶ | | | | | | | | | 0.005 | | | | |

¹ Participants were asked to recall their body fatness at ages 5, 10, and 20, using a nine-level drawing (Figure 1), where Level 1 corresponds to the leanest and Level 9 the most overweight.

² Average childhood and adolescent body fatness were the average of the levels at ages 5 and 10, and ages 10 and 20 respectively.

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³ Adjusted for smoking history [never, past, current], oral contraceptive use [never(ref), <3 years, 3-5 years, > 5years], postmenopausal hormone use (postmenopausal women only) [never, past, current – estrogen only, current – estrogen only, current – estrogen & progesterone / other], age at menopause (postmenopausal women only) [unknown, < 45 years, 45-< 47 years, 47 - <49 years (ref), 49- <51 years, 51- <53 years, 53+ years], family history of colon/rectal cancer, family history of endometrial cancer, height (inches; continuous), parity and age at last birth[Nulliparous, 1-2 & <30 yrs, 1-2 & 30 yrs, 3-4 & < 30 yrs, 3-4 & 30 yrs, 5 children], physical activity [adolescent & age 20 models: <21, 21-<36, 36-<53, 54-<81, 81+ METS/week; recent BMI model: <3, 3-<9, 9-<18, 18-<27, 27+ METS/week]

⁴ BMI: body mass index

⁵ Recent BMI models not adjusted for recent BMI

⁶ Wald test for interaction between body size and menopausal status (examined in base multivariate model)

Table 4

Age- and multivariable-adjusted hazard ratios and 95% confidence intervals for endometrial cancer by lifetime body fatness among postmenopausal participants, stratified by HT use

| | EVER USERS | | | | | NEVER USERS | | | | |
|--|------------------------|-----------------|--|--|------------------------|-----------------|--|--|--|--|
| | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | |
| Body fatness^J at age 5, Level | | | | | | | | | | |
| 1 | 144 / 180,840 | 1.00 | 1.00 | 1.00 | 66 / 126,607 | 1.00 | 1.00 | 1.00 | 1.00 | |
| 2 | 88 / 127,499 | 0.99 | 0.98 (0.75-1.29) | 0.98 (0.74-1.28) | 51 / 77,264 | 1.18 | 1.23 (0.84-1.81) | 1.19 (0.80-1.76) | 1.19 (0.80-1.76) | |
| 3 | 55 / 96,848 | 0.85 | 0.85 (0.62-1.17) | 0.81 (0.59-1.12) | 41 / 61,834 | 1.21 | 1.19 (0.80-1.79) | 0.97 (0.64-1.48) | 0.97 (0.64-1.48) | |
| 4 | 36 / 56,055 | 0.89 | 0.88 (0.61-1.28) | 0.79 (0.54-1.15) | 34 / 37,613 | 1.78 | 1.78 (1.16-2.73) | 1.30 (0.83-2.02) | 1.30 (0.83-2.02) | |
| 5+ | 33 / 36,514 | 1.26 | 1.27 (0.86-1.87) | 1.12 (0.76-1.66) | 14 / 26,915 | 0.95 | 0.89 (0.49-1.61) | 0.61 (0.33-1.12) | 0.61 (0.33-1.12) | |
| <i>P_{trend}</i> | | 0.89 | 0.88 | 0.56 | | 0.17 | 0.25 | 0.49 | 0.49 | |
| <i>P_{interaction}</i> ⁵ | | | | | | | | | 0.14 | |
| Body fatness^J at age 10, Level | | | | | | | | | | |
| 1 | 112 / 140,185 | 1.00 | 1.00 | 1.00 | 40 / 94,813 | 1.00 | 1.00 | 1.00 | 1.00 | |
| 2 | 93 / 137,784 | 0.93 | 0.94 (0.71-1.25) | 0.92 (0.69-1.21) | 56 / 86,585 | 1.39 | 1.42 (0.94-2.17) | 1.28 (0.84-1.96) | 1.28 (0.84-1.96) | |
| 3 | 58 / 93,847 | 0.89 | 0.90 (0.65-1.24) | 0.84 (0.60-1.16) | 40 / 62,074 | 1.36 | 1.34 (0.85-2.12) | 1.01 (0.63-1.61) | 1.01 (0.63-1.61) | |
| 4 | 37 / 66,716 | 0.80 | 0.80 (0.55-1.17) | 0.71 (0.48-1.03) | 34 / 45,490 | 1.78 | 1.69 (1.05-2.72) | 1.11 (0.67-1.82) | 1.11 (0.67-1.82) | |
| 5+ | 56 / 59,223 | 1.42 | 1.42 (1.02-1.97) | 1.21 (0.86-1.70) | 36 / 41,271 | 1.93 | 1.78 (1.11-2.85) | 1.06 (0.65-1.73) | 1.06 (0.65-1.73) | |
| <i>P_{trend}</i> | | 0.30 | 0.30 | 0.98 | | 0.003 | 0.01 | 0.92 | 0.92 | |
| <i>P_{interaction}</i> ⁵ | | | | | | | | | 0.03 | |
| Body fatness^J at age 20, Level | | | | | | | | | | |
| 1-2 | 151 / 198,137 | 1.00 | 1.00 | 1.00 | 57 / 127,424 | 1.00 | 1.00 | 1.00 | 1.00 | |
| 3 | 108 / 171,336 | 0.90 | 0.91 (0.70-1.16) | 0.84 (0.65-1.09) | 68 / 110,831 | 1.35 | 1.32 (0.92-1.90) | 1.08 (0.74-1.56) | 1.08 (0.74-1.56) | |
| 4 | 63 / 86,785 | 1.05 | 1.04 (0.77-1.40) | 0.90 (0.66-1.22) | 51 / 59,369 | 1.83 | 1.67 (1.12-2.49) | 1.03 (0.67-1.58) | 1.03 (0.67-1.58) | |
| 5+ | 34 / 41,498 | 1.15 | 1.13 (0.77-1.65) | 0.89 (0.60-1.33) | 30 / 32,610 | 2.08 | 1.72 (1.08-2.75) | 0.81 (0.48-1.35) | 0.81 (0.48-1.35) | |
| <i>P_{trend}</i> | | 0.54 | 0.60 | 0.42 | | <0.001 | 0.01 | 0.51 | 0.51 | |

| | | EVER USERS | | | | | | NEVER USERS | | | | | |
|--|---------------------|------------------------|-----------------|--|--|------------------------|-----------------|--|--|--|--------|--|--|
| | $P_{Interaction}^5$ | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | No. cases/person-years | Age-adjusted HR | Multivariate-adjusted HR ³ (95% CI) | Multivariate-adjusted HR ³ + recent BMI ⁴ (95% CI) | | | | |
| Average childhood body fatness (ages 5 – 10)², Level | | | | | | | | | | | 0.01 | | |
| 1-2 | | 204 / 272,896 | 1.00 | 1.00 | 1.00 | 94 / 179,987 | 1.00 | 1.00 | 1.00 | | | | |
| 2.5-3 | | 69 / 104,267 | 0.99 | 1.00 (0.76-1.32) | 0.95 (0.72-1.25) | 49 / 67,768 | 1.30 | 1.27 (0.89-1.82) | 1.02 (0.70-1.48) | | | | |
| 3.5-4.5 | | 50 / 87,104 | 0.86 | 0.85 (0.62-1.17) | 0.77 (0.56-1.05) | 48 / 57,618 | 1.65 | 1.55 (1.08-2.23) | 1.08 (0.73-1.58) | | | | |
| 5+ | | 33 / 33,488 | 1.45 | 1.45 (1.00-2.12) | 1.25 (0.85-1.84) | 15 / 24,859 | 1.12 | 1.03 (0.59-1.80) | 0.66 (0.36-1.15) | | | | |
| P_{trend} | | | 0.49 | 0.50 | 0.80 | | 0.05 | 0.12 | 0.41 | | | | |
| Average adolescent body fatness (ages 10 – 20)², Level | | | | | | | | | | | 0.12 | | |
| 1-2 | | 150 / 195,308 | 1.00 | 1.00 | 1.00 | 56 / 126,767 | 1.00 | 1.00 | 1.00 | | | | |
| 2.5-3 | | 95 / 151,533 | 0.90 | 0.91 (0.70-1.18) | 0.85 (0.65-1.11) | 60 / 97,753 | 1.37 | 1.35 (0.93-1.97) | 1.16 (0.79-1.70) | | | | |
| 3.5-4.5 | | 83 / 122,339 | 0.99 | 1.00 (0.76-1.31) | 0.87 (0.66-1.15) | 69 / 84,007 | 1.83 | 1.73 (1.19-2.50) | 1.12 (0.76-1.66) | | | | |
| 5+ | | 28 / 28,575 | 1.47 | 1.42 (0.94-2.15) | 1.12 (0.73-1.72) | 21 / 21,709 | 2.14 | 1.80 (1.06-3.05) | 0.88 (0.50-1.56) | | | | |
| P_{trend} | | | 0.34 | 0.37 | 0.72 | | <0.001 | 0.002 | 0.95 | | | | |
| Recent BMI, kg/m² | | | | | | | | | | | 0.01 | | |
| 24.9 | | 150 / 243,398 | 1.00 | 1.00 | N/A ⁵ | 26 / 138,819 | 1.00 | 1.00 | N/A ⁵ | | | | |
| 25.0-29.9 | | 111 / 156,920 | 1.16 | 1.16 (0.90-1.50) | | 56 / 108,637 | 2.51 | 2.35 (1.46-3.78) | | | | | |
| 30.0-34.9 | | 59 / 63,369 | 1.65 | 1.64 (1.19-2.26) | | 53 / 51,279 | 4.95 | 4.25 (2.65-7.13) | | | | | |
| 35.0 | | 36 / 34,068 | 2.35 | 2.23 (1.49-3.34) | | 71 / 31,499 | 11.15 | 9.31 (5.64-15.35) | | | | | |
| P_{trend} | | | <0.001 | <0.001 | | | <0.001 | <0.001 | | | | | |
| $P_{Interaction}^6$ | | | | | | | | | | | <0.001 | | |

¹ Participants were asked to recall their body fatness at ages 5, 10, and 20, using a nine-level drawing (Figure 1), where Level 1 corresponds to the leanest and Level 9 the most overweight.

² Average childhood and adolescent body fatness were the average of the levels at ages 5 and 10, and ages 10 and 20 respectively.

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⁵ Adjusted for smoking history [never, past, current], oral contraceptive use [never, <3 years, 3-5 years, > 5years], postmenopausal hormone use (ever-users only) [past (ref), current – estrogen only, current – estrogen & progesterone / other], age at menopause [unknown, < 45, 45-< 47, 47 - <49, 49-<51, 51- <53, 53+ years], birth weight [<5.5, 5.5-<7, 7-8.4, 8-5-9.9, 10 lb], family history of colon/rectal cancer, family history of endometrial cancer, height (inches; continuous), parity and age at last birth [Nulliparous, 1-2 & <30 yrs, 1-2 & 30 yrs, 3-4 & < 30 yrs, 3-4 & 30 yrs, 5 children], physical activity [adolescent & age 20 models: <21, 21-<36, 36-<53, 54-<81, 81+ METS/week; recent BMI model: <3, 3-<9, 9-<18, 18-<27, 27+ METS/week]

⁴ BMI: body mass index

⁵ Recent BMI models not adjusted for recent BMI

⁶ Wald test for interaction between body size and postmenopausal hormone use (examined in base multivariate model).

Table 5

Supplemental Table 1. Multivariable adjusted-hazard ratios and 95% confidence intervals for endometrial cancer by early life body fatness among NHS (1988-2010) and NHS II (1989 – 2009) participants

| | | NHS | | | | NHS II | | | |
|--|------------------------|---|--|------------------------|---|--|------------------|------|--|
| | No. cases/person-years | Multivariate-adjusted HR ³ (95% CI) | Multivariate adjusted HR ³ + current BMI ⁴ (95% CI) | No. cases/person-years | Multivariate-adjusted HR ³ (95% CI) | Multivariate adjusted HR ³ + current BMI ⁴ (95% CI) | | | |
| Body fatness¹ at age 5, Level | | | | | | | | | |
| 1 | 236 / 321,965 | 1.00 | 1.00 | 28 / 409,534 | 1.00 | 1.00 | 1.00 | 1.00 | |
| 2 | 145 / 187,983 | 1.08 (0.87-1.33) | 1.06 (0.85-1.30) | 48 / 543,662 | 1.44 (0.90-2.31) | 1.39 (0.87-2.22) | 1.39 (0.87-2.22) | | |
| 3 | 89 / 144,263 | 0.89 (0.70-1.14) | 0.80 (0.62-1.02) | 47 / 409,546 | 1.73 (1.08-2.77) | 1.45 (0.90-2.33) | 1.45 (0.90-2.33) | | |
| 4 | 70 / 87,130 | 1.11 (0.86-1.47) | 0.92 (0.70-1.20) | 25 / 216,892 | 1.65 (0.95-2.84) | 1.20 (0.70-2.08) | 1.20 (0.70-2.08) | | |
| 5+ | 50 / 61,578 | 1.13 (0.83-1.54) | 0.85 (0.62-1.17) | 19 / 115,273 | 2.02 (1.12-3.64) | 1.27 (0.69-2.34) | 1.27 (0.69-2.34) | | |
| <i>P trend</i> | | 0.54 | 0.13 | | 0.01 | 0.55 | 0.55 | | |
| <i>P interaction</i> ⁶ | | | | | 0.03 | | | | |
| Body fatness¹ at age 10, Level | | | | | | | | | |
| 1 | 169 / 243,447 | 1.00 | 1.00 | 21 / 310,967 | 1.00 | 1.00 | 1.00 | 1.00 | |
| 2 | 160 / 212,542 | 1.12 (0.90-1.39) | 1.06 (0.85-1.31) | 36 / 523,851 | 1.14 (0.66-1.96) | 1.04 (0.60-1.78) | 1.04 (0.60-1.78) | | |
| 3 | 101 / 144,897 | 1.07 (0.83-1.37) | 0.91 (0.71-1.17) | 46 / 387,750 | 1.88 (1.11-3.15) | 1.43 (0.85-2.42) | 1.43 (0.85-2.42) | | |
| 4 | 74 / 105,684 | 1.07 (0.81-1.41) | 0.82 (0.62-1.09) | 26 / 268,800 | 1.42 (0.79-2.53) | 0.94 (0.52-1.70) | 0.94 (0.52-1.70) | | |
| 5+ | 86 / 96,349 | 1.36 (1.04-1.77) | 0.97 (0.74-1.28) | 38 / 203,538 | 2.34 (1.36-4.03) | 1.34 (0.76-2.36) | 1.34 (0.76-2.36) | | |
| <i>P trend</i> | | 0.07 | 0.32 | | 0.001 | 0.43 | 0.43 | | |
| <i>P interaction</i> ⁶ | | | | | 0.01 | | | | |
| Body fatness¹ at age 20, Level | | | | | | | | | |
| 1-2 | 226 / 325,929 | 1.00 | 1.00 | 44 / 513,813 | 1.00 | 1.00 | 1.00 | 1.00 | |
| 3 | 183 / 271,833 | 1.02 (0.83-1.24) | 0.89 (0.73-1.08) | 39 / 644,085 | 0.76 (0.49-1.17) | 0.61 (0.39-0.95) | 0.61 (0.39-0.95) | | |
| 4 | 112 / 138,461 | 1.20 (0.96-1.51) | 0.91 (0.72-1.15) | 46 / 353,744 | 1.57 (1.03-2.38) | 1.00 (0.64-1.55) | 1.00 (0.64-1.55) | | |
| 5+ | 69 / 66,695 | 1.43 (1.08-1.88) | 0.89 (0.67-1.20) | 38 / 183,263 | 2.15 (1.36-3.40) | 0.93 (0.55-1.59) | 0.93 (0.55-1.59) | | |
| <i>P trend</i> | | 0.01 | 0.36 | | <0.001 | 0.75 | 0.75 | | |
| <i>P interaction</i> ⁶ | | | | | 0.01 | | | | |

| | | NHS I | | | NHS II | | |
|--|------------------------|---|--|------------------------|---|--|--|
| | No. cases/person-years | Multivariate-adjusted HR ³ (95% CI) | Multivariate adjusted HR ³ + current BMI ⁴ (95% CI) | No. cases/person-years | Multivariate-adjusted HR ³ (95% CI) | Multivariate adjusted HR ³ + current BMI ⁴ (95% CI) | |
| Average childhood body fatness (ages 5 – 10)², Level | | | | | | | |
| 1-2 | 327 / 452,126 | 1.00 | 1.00 | 54 / 810,829 | 1.00 | 1.00 | |
| 2.5-3 | 117 / 159,702 | 1.05 (0.85-1.30) | 0.93 (0.75-1.16) | 51 / 430,074 | 1.77 (1.21-2.61) | 1.48 (1.00-2.18) | |
| 3.5-4.5 | 96 / 134,150 | 1.03 (0.82-1.30) | 0.84 (0.66-1.05) | 42 / 349,457 | 1.62 (1.08-2.44) | 1.13 (0.74-1.72) | |
| 5+ | 50 / 56,941 | 1.25 (0.93-1.69) | 0.90 (0.66-1.22) | 20 / 104,545 | 2.19 (1.30-3.69) | 1.29 (0.75-2.23) | |
| <i>P trend</i> | | 0.23 | 0.16 | | 0.001 | 0.43 | |
| <i>P interaction</i> ⁶ | | | | | 0.01 | | |
| Average adolescent body fatness (ages 10 – 20)², Level | | | | | | | |
| 1-2 | 223 / 325,593 | 1.00 | 1.00 | 38 / 490,419 | 1.00 | 1.00 | |
| 2.5-3 | 168 / 236,570 | 1.07 (0.88-1.32) | 0.96 (0.78-1.18) | 40 / 594,805 | 0.95 (0.61-1.48) | 0.79 (0.50-1.24) | |
| 3.5-4.5 | 148 / 193,645 | 1.18 (0.95-1.45) | 0.90 (0.73-1.12) | 63 / 504,038 | 1.62 (1.08-2.45) | 1.01 (0.65-1.57) | |
| 5+ | 51 / 47,111 | 1.56 (1.14-2.13) | 0.97 (0.70-1.33) | 26 / 105,643 | 2.44 (1.45-4.12) | 1.09 (0.61-1.94) | |
| <i>P trend</i> | | 0.01 | 0.49 | | <0.001 | 0.62 | |
| <i>P interaction</i> ⁶ | | | | | 0.01 | | |
| Recent BMI, kg/m² | | | | | | | |
| 24.9 | 190 / 381,392 | 1.00 | N/A ⁵ | 52 / 942,295 | 1.00 | N/A ⁵ | |
| 25.0-29.9 | 168 / 260,339 | 1.26 (1.02-1.56) | | 34 / 419,079 | 1.17 (0.75-1.81) | | |
| 30.0-34.9 | 121 / 107,586 | 2.18 (1.71-2.78) | | 29 / 187,606 | 2.00 (1.25-3.20) | | |
| 35.0 | 111 / 53,602 | 4.14 (3.18-5.39) | | 52 / 145,926 | 3.95 (2.55-6.11) | | |
| <i>P trend</i> | | <0.001 | | | <0.001 | | |
| <i>P interaction</i> ⁶ | | | | | 0.001 | | |

¹ Participants were asked to recall their body fatness at ages 5, 10, and 20, using a nine-level drawing (Figure 1), where Level 1 corresponds to the leanest and Level 9 the most overweight.

² Average childhood and adolescent body fatness were the average of the levels at ages 5 and 10, and ages 10 and 20 respectively.

³ Adjusted for pack-years of smoking [0,>0-20,>20-40,>40] –NHS; [never, past, current – NHS II], oral contraceptive use [never, <3 years, 3-5 years, > 5years], HT use [premenopausal, post-menopausal – never; postmenopausal – past; post-menopausal current – estrogen only; postmenopausal current – estrogen + progesterone – NHS]; postmenopausal status [pre/post], postmenopausal hormone use [never/ever estrogen; never/ever estrogen + progesterone; never/ever other] – NHS II, age at menopause [premenopausal/unknown, < 45 years, 45-< 47 years, 47 - <49 years, 49- <51, 51- <53 years, 53+ years],

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family history of colon/rectal cancer, family history of endometrial cancer, height (inches; continuous), parity and age at last birth [Nulliparous, 1-2 & <30 yrs, 1-2 & 30 yrs, 3-4 & <30 yrs, 3-4 & 30 yrs, 5 children], physical activity [adolescent & age 20 models: <21, 21-<36, 36-<53, 54-<81, 81+; current BMI model: <3, 3-<9, 9-<18, 18-<27, 27+ METS/week]

⁴BMI: body mass index

⁵Recent BMI models not adjusted for recent BMI.

⁶Wald test for heterogeneity between cohorts by body size (examined in base multivariate model).