Body size and composition, physical activity and sedentary time in relation to endogenous hormones in premenopausal and postmenopausal women: Findings from the UK Biobank

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Abstract

Anthropometric and lifestyle factors may influence cancer risks through hormonal changes. We investigated cross-sectional associations between body size and composition, physical activity and sedentary time and serum concentrations of oestradiol (premenopausal women only), testosterone, sex hormone binding globulin (SHBG) and insulin-like growth factor-I (IGF-I) in 20,758 premenopausal and 71,101 postmenopausal women in UK Biobank. In premenopausal women, higher BMI (body mass index) was associated with a lower concentration of total oestradiol (15% difference in the highest vs lowest BMI group) and a higher concentration of calculated free oestradiol (22%). In both premenopausal and postmenopausal women, higher BMI was associated with higher concentrations of total and calculated free testosterone (premenopausal 29% and 113%, postmenopausal 39% and 126%, respectively) and lower concentrations of SHBG and IGF-I (premenopausal 51% and 14%, postmenopausal 51% and 12%, respectively). Similar associations were observed with waist to height ratio, waist to hip ratio and body or trunk fat mass. Self-reported physical activity was associated with somewhat lower concentrations of total and calculated free testosterone (premenopausal 10% difference [free testosterone], postmenopausal 5% and 11% difference respectively in the most vs least active group) and a higher concentration of SHBG (premenopausal 11%, postmenopausal 10%), and the opposite was true for self-reported sedentary time. The associations were slightly stronger with accelerometer-measured physical activity, but were attenuated after adjustment for BMI. Overall, our study confirms strong associations of hormones and SHBG with anthropometric factors. The associations with physical activity and sedentary time were at most modest.

Keywords

anthropometry, hormone, physical activity, sedentary behaviour, UK Biobank

Abbreviations: BMI, body mass index; IGF-I, insulin-like growth factor-I; IPAQ, International Physical Activity Questionnaire; METs, metabolic equivalents; SHBG, sex hormone binding globulin.
1 | INTRODUCTION

Anthropometric and lifestyle factors influence cancer risks and outcomes. Overweight and obesity increase the risk of several cancers, including hormone-related cancers in women, except for premenopausal breast cancer, for which obesity is associated with a lower risk. In contrast, physical activity, one of the most modifiable lifestyle factors, appears to reduce the risk of several cancers, possibly independently of adiposity. The associations between obesity, physical activity and cancer risk may be explained by a number of biological mechanisms including changes in hormones, metabolism, immune function and inflammation.

Endogenous hormones play an important role in carcinogenesis by promoting cell proliferation and therefore increasing the chances of random genetic errors. Circulating sex hormones such as oestrogens and androgens, and growth factors such as insulin-like growth factor I (IGF-I), have been associated with an increased risk of several cancers including breast and gynaecological cancers in women, whereas sex hormone-binding globulin (SHBG) is inversely associated with the risk. As these hormone-dependent cancers are also related to obesity and physical activity, endogenous hormones, if proven to be associated with these lifestyle factors, may mediate the influence of the latter on cancer risk.

Obesity and physical activity have been reported to influence circulating sex hormones and growth factors. However, the evidence to date is not conclusive, particularly in premenopausal women due to small sample size as well as the cyclic nature of hormonal fluctuations before menopause. Given that the proliferative rate of mammary epithelial cells is highest in the mid-luteal phase, menstrual cycle-specific analyses may provide insights into how obesity and physical activity influence the risk of premenopausal breast cancer. We therefore investigated the associations between body size and composition, physical activity and sedentary time and serum concentrations of oestradiol, testosterone, SHBG and IGF-I in both premenopausal and postmenopausal women, using data from UK Biobank; with data on hormones for over 90 000 women this is as far as we are aware the largest dataset on this topic, which enabled us to undertake subgroup analyses by phase of the menstrual cycle.

What’s new?

Circulating concentrations of oestrogen and androgen hormones are associated with increased risk of breast and some gynaecological cancers in women. These same cancer types are also influenced by obesity and possibly physical activity, though whether the impacts of the latter factors are mediated by hormones remains uncertain. In this investigation of endogenous hormones, body composition, physical activity, and sedentary time in pre- and post-menopausal women, strong associations were found between adult anthropometric factors, hormones, and sex hormone binding globulin. Associations were modest for physical activity and sedentary time. The findings support the hypothesis that sex hormones mediate the impacts of anthropometric factors on risk for some cancers in women, but suggest that the possible protective effects of physical activity against cancer might be mediated by pathways other than sex hormones.

2 | MATERIALS AND METHODS

2.1 | Data source

Data were extracted from UK Biobank, a large prospective cohort study (project reference number 3248, approved August 2013). Study design and methodology has been described elsewhere. This research is covered by the approval of the UK Biobank research ethics committee (approval number 11/NW/0382).

2.2 | Study participants

UK Biobank involves about 500 000 adults, including over 270 000 women, aged between 40 and 69 years when recruited in 22 assessment centres between 2006 and 2010. During the initial assessment centre visit, participants completed a touchscreen questionnaire that included questions on sociodemographics, family history and early life factors, lifestyle and environment, psychosocial factors, health and medical history and sex-specific factors. Participants also underwent physical measurements, including body size and composition, and provided blood and urine samples.

For the current analyses, women were categorised as premenopausal if they answered ‘no’ to the question ‘Have you had your menopause (period stopped)?’ and were younger than 55 years of age, or answered ‘not sure’ or did not answer and were younger than 50 years of age, and had no history of hormone replacement therapy use, hysterectomy or bilateral oophorectomy. They were categorised as postmenopausal if they reported ‘yes’ to the above question, or answered ‘not sure’ or did not answer and were 55 years or older, or reported a bilateral oophorectomy. Women were excluded from the analyses if they reported being pregnant or currently using oral contraceptive pills (premenopausal), currently using hormone replacement therapy (postmenopausal), had a prior cancer diagnosis except for nonmelanoma skin cancer (identified from self-reports as well as linkage to national cancer registries), had a prior diagnosis of endocrine or gynaecological disorder, or had missing data on time since last menstrual period, study exposures or outcomes (Figure S1).

2.3 | Exposure assessment

2.3.1 | Body size and composition

Height was measured using the Seca 202 height measure (Seca, Hamburg, Germany), and waist (at the natural indent) and hip (widest
point) circumferences were measured over light clothes with the Seca-200 tape measure (Seca, Hamburg, Germany). Weight and bio-impedance measures were taken using the Tanita BC418MA body composition analyser (Tanita, Tokyo, Japan), from which body and trunk fat masses were estimated. Body mass index (BMI) was calculated as weight in kilogrammes divided by the square of height in meters.

2.3.2 | Comparative body size and height at Age 10

Comparative body size and height were assessed by asking the women how they would describe themselves compared to average when they were 10 years old.

2.3.3 | Physical activity

Self-reported physical activity was assessed using questions adapted from the International Physical Activity Questionnaire (IPAQ) short form which is a validated survey instrument and covers the frequency and duration of three levels of activity (walking, moderate and vigorous). Data processing guidelines published by IPAQ were followed and women who had a sum of all three activities greater than 6720 minutes per week were excluded (Figure S1). Time spent in television or using a computer (excluding using a computer at work). Sedentary time was measured as the total number of hours watching television or using a computer (excluding using a computer at work).

2.3.4 | Sedentary time

Sedentary time was measured as the total number of hours watching television or using a computer (excluding using a computer at work).

2.4 | Hormone assays

Hormones and SHBG were measured using chemiluminescent immunoassays in UK Biobank’s purpose-built facility in Stockport, UK. Serum concentrations of oestradiol (reported here only for premenopausal women), testosterone and SHBG were measured on the UniCel Dxi 800 (Beckman Coulter, Brea, USA) and the concentration of IGF-I was measured on the Liaison XL (DiaSorin, Saluggia, Italy). If the test result was missing due to a very low serum concentration, the concentration was set at half the minimum reportable value. The minimum reportable concentrations were 175 pmol/L for oestradiol, 0.35 nmol/L for testosterone, 0.33 nmol/L for SHBG and 1.30 nmol/L for IGF-I. Concentrations of free oestradiol and testosterone were calculated assuming that the binding of these hormones to serum albumin and SHBG follows the law of mass action.

Hormones and SHBG were also measured in repeat blood samples collected from a subsample of participants in 2012-2013, on average 4 years after baseline. There were significant correlations (P < .0001) between baseline and repeated measures of testosterone (r = .47; n = 3112), SHBG (r = .80; n = 2703) and IGF-I (r = .76; n = 3140); for oestradiol, it was not possible to demonstrate correlations over time because few of the repeat samples were collected in the same phase of the menstrual cycle as the baseline sample, and many women became peri-menopausal during follow-up.

2.5 | Statistical analysis

Hormone and SHBG concentrations were logarithmically transformed. Geometric mean concentrations were compared across exposure categories using multivariable regression analysis, and linear trends were tested using orthogonal polynomial contrasts that partition the effect of exposure into its polynomial components. Analyses were undertaken separately for premenopausal and postmenopausal women. For premenopausal women, analyses were adjusted for age at recruitment (in 2-year groups), phase of menstrual cycle (early follicular—Days 0-5, late follicular—Days 6-10, mid-cycle—Days 11-14, early luteal—Days 15-18, mid-luteal—Days 19-24 and late luteal—Days ≥25 as categorised previously), ethnicity (White, Black, Asian and mixed/others), time since last birth (nulliparous, 1-3 years, >4 years), time since last oral contraceptive pill use (never, 1-5 years, 6-10 years, 11-20 years and ≥21 years), smoking (never, past, current), alcohol use (three times a month or less, 1-4 times a week and daily or almost daily), quintiles of Townsend deprivation index and region of recruitment (Scotland, North-East England, North-West England, Yorkshire and the Humber, East Midlands, West Midlands, Wales, South-West England, South-East England and London). Sensitivity analyses were undertaken by restricting the sample to women aged under 45 years (n = 10 024). For postmenopausal women, the models included age at recruitment (in five-year groups), ethnicity (as above), age at menopause (in 5-year groups), time since last hormone replacement therapy use (never, 1-5 years, 6-10 years and ≥11 years), smoking (as above), alcohol use (as above), quintiles of Townsend deprivation index and region (as above) as covariates. For both premenopausal and postmenopausal women, results further adjusted for BMI were also presented for the
associations between the exposures of interest (other than BMI) and hormone concentrations. As oestradiol concentrations vary considerably throughout the menstrual cycle in premenopausal women, subgroup analyses by phase of the menstrual cycle were undertaken. STATA 15.1 (StataCorp, College Station, Texas) was used for all analyses.

3 | RESULTS

In total, 20 758 premenopausal and 71 101 postmenopausal women were included in the analyses, of whom 4803 (23%) and 15 469 (22%) respectively had accelerometer data. Table 1 presents characteristics of the study participants.

| TABLE 1 | Participant characteristics |
|---------|----------------------------|
|         | Premenopausal | Postmenopausal |
|         | All | Available accelerometer data | All | Available accelerometer data |
| Number of participants | 20 758 | 4803 | 71 101 | 15 469 |
| Age at recruitment (years), mean (SD) | 44.7 (2.7) | 44.7 (2.7) | 60.0 (5.3) | 59.5 (5.1) |
| White, % | 92.3 | 94.6 | 96.4 | 97.6 |
| Townsend deprivation scores, median (IQR) | −2.0 (4.3) | −2.2 (4.1) | −2.4 (3.7) | −2.5 (3.4) |
| Age at menarche, mean (SD) | 13.1 (1.6) | 13.1 (1.5) | 13.0 (1.6) | 12.9 (1.5) |
| Nulliparous, % | 26.7 | 28.5 | 16.0 | 18.4 |
| Age at first birth (years), mean (SD) | 28.3 (5.4) | 29.0 (5.2) | 25.8 (4.9) | 26.6 (4.9) |
| Age at last birth (years), mean (SD) | 32.0 (5.1) | 32.5 (4.8) | 29.9 (5.0) | 30.4 (5.0) |
| Age at menopause (years), mean (SD) | 49.9 (5.0) | 50.2 (4.6) |
| Past use of oral contraceptive, % | 88.5 | 88.9 |
| Time since oral contraceptive use (years), mean (SD) | 14.4 (7.0) | 14.5 (7.0) |
| Past use of hormone replacement therapy, % | 43.3 | 42.4 |
| Time since hormone replacement therapy use (years), mean (SD) | 7.4 (4.9) | 7.0 (4.5) |
| Current smoker, % | 10.3 | 7.7 | 7.4 | 4.9 |
| One or more drinks weekly, % | 66.9 | 70.2 | 66.0 | 70.9 |
| Eat at least one tablespoon of salad or cooked or raw vegetable per day, % | 98.0 | 98.6 | 98.9 | 99.3 |
| Eat at least one piece of fresh or dried fruit per day, % | 92.7 | 93.7 | 96.0 | 96.9 |
| Eat meat at least once a week, % | 86.9 | 85.1 | 89.4 | 87.4 |
| Eat fish at least once a week, % | 71.6 | 71.3 | 81.2 | 80.9 |
| Eat eggs, dairy products, wheat products and sugar, % | 87.8 | 89.8 | 76.4 | 79.8 |
| Slices of bread intake per week, mean (SD) | 9.4 (7.0) | 9.5 (7.0) | 9.8 (7.2) | 9.6 (7.1) |
| Bowls of cereal intake per week, mean (SD) | 3.6 (4.0) | 3.8 (4.0) | 4.3 (3.9) | 4.4 (3.9) |
| Use butter, % | 42.4 | 43.9 | 37.5 | 38.6 |
| Body mass index (kg/m2), mean (SD) | 25.9 (5.0) | 25.3 (4.6) | 26.7 (4.7) | 26.0 (4.5) |
| Height (cm), mean (SD) | 164.5 (6.3) | 164.9 (6.2) | 162.2 (6.1) | 163.0 (6.1) |
| Waist to height ratio, mean (SD) | 0.49 (0.07) | 0.48 (0.07) | 0.52 (0.07) | 0.51 (0.07) |
| Waist to hip ratio, mean (SD) | 0.79 (0.07) | 0.79 (0.06) | 0.82 (0.07) | 0.81 (0.07) |
| Body fat mass (kg), mean (SD) | 24.7 (10.0) | 23.5 (9.4) | 26.4 (9.3) | 25.3 (8.9) |
| Trunk fat mass (kg), mean (SD) | 12.5 (5.3) | 11.9 (5.1) | 13.4 (4.9) | 12.9 (4.8) |
| About average body size at age 10, % | 50.2 | 52.0 | 52.2 | 52.9 |
| About average height at age 10, % | 51.7 | 51.0 | 53.7 | 51.7 |
| Self-reported physical activity (MET-hours/week), median (IQR) | 29.1 (40.2) | 29.8 (37.2) | 30.6 (45.2) | 30.6 (42.6) |
| Accelerometer-measured physical activity (milligravity), mean (SD) | 31.6 (8.7) | 31.6 (8.7) | 28.0 (7.6) |
| Sedentary time, median (IQR) | 3.0 (2.0) | 3.0 (2.0) | 3.5 (2.5) | 3.0 (2.5) |
**TABLE 2**  Adjusted geometric means of serum hormones and SHBG in premenopausal women

| n     | Median (IQR) | Total oestradiol, pmol/L | Calculated free oestradiol, pmol/L | Total testosterone, nmol/L | Calculated free testosterone, pmol/L | SHBG, nmol/L | IGF-I, nmol/L |
|-------|--------------|---------------------------|------------------------------------|-----------------------------|--------------------------------------|-------------|--------------|
|       |              | Geometric mean            | P<sub>hetere</sub>              | Geometric mean             | P<sub>hetere</sub>              | Geometric mean | P<sub>hetere</sub> | Geometric mean | P<sub>hetere</sub> | Geometric mean | P<sub>hetere</sub> | Geometric mean | P<sub>hetere</sub> |
| BMI (kg/m²) |              |                           |                                   |                            |                                      |              |              |                       |                         |                        |              |              |                        |                         |
| <22.5  | 5270         | 21.2 (1.7)                | 348.85                            | <.0001                      | 3.61                                 | <.0001            | 0.91            | <.0001              | 10.72                   | <.0001                  | 8.72        | <.0001        | 77.52                  | <.0001                  |
| 22.5-24.9 | 5249         | 23.7 (1.2)                | 338.21                            | <.0001                      | 3.76                                 | <.0001            | 0.98            | <.0001              | 10.41                   | <.0001                  | 68.18        | <.0001        | 61.00                   | <.0001                  |
| 25.0-27.4 | 4268         | 26.1 (1.2)                | 329.47                            | <.0001                      | 3.91                                 | 1.03               | 11.95           |                      | 23.72                   |                         |                        |              |              |                        |                         |
| 27.5-29.9 | 2445         | 28.6 (1.3)                | 327.65                            | <.0001                      | 4.18                                 | 1.10               | 14.04           |                      | 23.34                   |                         |                        |              |              |                        |                         |
| 30.0-34.9 | 2357         | 31.9 (2.5)                | 302.59                            | <.0001                      | 4.14                                 | 1.10               | 15.59           |                      | 22.32                   |                         |                        |              |              |                        |                         |
| 35+     | 1169         | 38.1 (4.6)                | 295.82                            | <.0001                      | 4.39                                 | 1.17               | 18.54           |                      | 20.08                   |                         |                        |              |              |                        |                         |
| Height (cm) |              |                           |                                   |                            |                                      |              |              |                       |                         |                        |              |              |                        |                         |
| Q1     | 5379         | 157.0 (4.0)               | 331.38                            | <.0001                      | 3.92                                 | <.0001            | 1.02            | .03                  | 11.79                   | <.0001                  | 60.19        | <.0001        | 61.06                   | <.0001                  |
| Q2     | 5014         | 163.0 (2.0)               | 337.73                            | <.0001                      | 3.96                                 | .06               | 1.02            | .04                  | 11.61                   | <.0001                  | 61.06        | <.0001        | 61.06                   | <.0001                  |
| Q3     | 6060         | 167.0 (2.0)               | 325.22                            | <.0001                      | 3.79                                 | 1.00               | 11.33           |                      | 23.37                   |                         |                        |              |              |                        |                         |
| Q4     | 4305         | 172.0 (4.0)               | 331.16                            | <.0001                      | 3.85                                 | 0.99               | 11.12           |                      | 23.61                   |                         |                        |              |              |                        |                         |
| Waist to height ratio |              |                           |                                   |                            |                                      |              |              |                       |                         |                        |              |              |                        |                         |
| Q1     | 5193         | 0.42 (0.03)               | 358.11                            | <.0001                      | 3.70                                 | <.0001            | 0.94            | <.0001              | 8.96                    | <.0001                  | 78.19        | <.0001        | 74.71                   | <.0001                  |
| Q2     | 5186         | 0.46 (0.02)               | 336.79                            | <.0001                      | 3.74                                 | <.0001            | 0.97            | <.0001              | 10.22                   | <.0001                  | 68.47        | <.0001        | 66.38                   | <.0001                  |
| Q3     | 5193         | 0.50 (0.03)               | 325.23                            | <.0001                      | 3.90                                 | 1.03               | 12.15           |                      | 23.59                   |                         |                        |              |              |                        |                         |
| Q4     | 5186         | 0.58 (0.07)               | 306.14                            | <.0001                      | 4.18                                 | 1.10               | 15.57           |                      | 22.14                   |                         |                        |              |              |                        |                         |
| Waist to hip ratio |              |                           |                                   |                            |                                      |              |              |                       |                         |                        |              |              |                        |                         |
| Q1     | 5221         | 0.72 (0.03)               | 351.45                            | <.0001                      | 3.73                                 | <.0001            | 0.97            | <.0001              | 9.64                    | <.0001                  | 74.71        | <.0001        | 74.71                   | <.0001                  |
| Q2     | 5225         | 0.77 (0.02)               | 343.20                            | <.0001                      | 3.87                                 | 1.00               | 10.82           | <.0001              | 66.38                   | <.0001                  | 74.71        | <.0001        | 74.71                   | <.0001                  |
| Q3     | 5126         | 0.81 (0.02)               | 319.30                            | <.0001                      | 3.84                                 | 1.01               | 11.89           |                      | 24.33                   |                         |                        |              |              |                        |                         |
| Q4     | 5186         | 0.87 (0.05)               | 311.49                            | <.0001                      | 4.07                                 | 1.05               | 13.99           |                      | 22.66                   |                         |                        |              |              |                        |                         |
| Body fat mass (kg) |              |                           |                                   |                            |                                      |              |              |                       |                         |                        |              |              |                        |                         |
| Q1     | 5270         | 15.0 (3.6)                | 352.00                            | <.0001                      | 3.68                                 | <.0001            | 0.92            | <.0001              | 8.91                    | <.0001                  | 76.32        | <.0001        | 76.32                   | <.0001                  |
| Q2     | 5117         | 20.2 (2.3)                | 337.85                            | <.0001                      | 3.76                                 | <.0001            | 0.99            | <.0001              | 10.49                   | <.0001                  | 68.17        | <.0001        | 68.17                   | <.0001                  |
| Q3     | 5189         | 25.6 (3.2)                | 328.99                            | <.0001                      | 3.92                                 | 1.03               | 11.97           |                      | 23.64                   |                         |                        |              |              |                        |                         |
| Q4     | 5182         | 35.9 (9.9)                | 306.72                            | <.0001                      | 4.17                                 | 1.11               | 15.52           |                      | 22.13                   |                         |                        |              |              |                        |                         |
| Trunk fat mass (kg) |              |                           |                                   |                            |                                      |              |              |                       |                         |                        |              |              |                        |                         |
| Q1     | 5315         | 7.0 (2.3)                 | 350.76                            | <.0001                      | 3.69                                 | <.0001            | 0.92            | <.0001              | 9.06                    | <.0001                  | 75.33        | <.0001        | 75.33                   | <.0001                  |
| Q2     | 5220         | 10.2 (1.5)                | 338.68                            | <.0001                      | 3.78                                 | <.0001            | 0.99            | <.0001              | 10.57                   | <.0001                  | 67.64        | <.0001        | 67.64                   | <.0001                  |
| TABLE 2 | (Continued) |
|---|---|

| Q3 | 5054 | 13.3 (1.7) | 328.71 | 3.92 | 1.03 | 11.99 | 59.32 | 23.63 |
| Q4 | 5169 | 18.7 (5.0) | 306.92 | 4.13 | 1.10 | 15.21 | 46.54 | 22.16 |

Comparative body size at age 10

| Thinner | 6608 | 23.8 (50) | 332.66 <.0001 | 3.88 <.0001 | 1.01 .07 | 11.40 <.0001 | 61.56 <.0001 | 23.38 <.0001 |
| About average | 10 429 | 24.8 (52) | 332.52 .1 | 3.85 .3 | 1.01 .1 | 11.24 <.0001 | 62.95 <.0001 | 23.28 <.0001 |
| Plumper | 3721 | 27.5 (7.4) | 324.10 | 3.95 | 1.02 | 12.28 | 56.77 | 22.71 |

Comparative height at age 10

| Shorter | 4306 | 158.0 (6.5) | 334.97 <.0001 | 3.89 <.0001 | 1.00 .2 | 11.26 <.0001 | 62.44 <.0001 | 22.82 <.0001 |
| About average | 10 728 | 164.0 (6.0) | 329.20 .5 | 3.85 .5 | 1.01 .3 | 11.43 .007 | 61.59 .001 | 23.22 <.0001 |
| Taller | 5724 | 170.0 (6.4) | 331.55 | 3.92 | 1.01 | 11.70 | 60.13 | 23.47 |

Self-reported physical activity (MET-hours/week)

| Q1 | 5193 | 7.3 (6.7) | 332.64 <.0001 | 4.02 <.0001 | 1.03 .003 | 12.28 <.0001 | 57.52 <.0001 | 23.01 <.0001 |
| Q2 | 5204 | 20.9 (7.3) | 328.22 .5 | 3.86 .004 | 1.00 .008 | 11.42 <.0001 | 61.00 <.0001 | 23.25 .03 |
| Q3 | 5172 | 39.5 (12.3) | 326.39 | 3.77 | 1.01 | 11.20 | 63.14 | 23.35 |
| Q4 | 5189 | 82.6 (45.5) | 337.00 | 3.86 | 1.00 | 11.01 | 63.98 | 23.22 |

Accelerometer-measured PA (milli-gravity)

| Q1 | 1201 | 22.7 (3.5) | 341.02 <.0001 | 4.09 <.0001 | 1.07 <.0001 | 12.56 <.0001 | 58.67 <.0001 | 23.36 <.0001 |
| Q2 | 1202 | 28.1 (2.3) | 334.56 .9 | 3.93 .005 | 1.02 <.0001 | 11.64 <.0001 | 60.99 <.0001 | 23.63 .5 |
| Q3 | 1200 | 33.1 (2.8) | 336.80 | 3.83 | 0.99 | 10.78 | 64.92 | 23.68 |
| Q4 | 1200 | 41.0 (7.5) | 338.04 | 3.74 | 0.92 | 9.59 | 69.14 | 23.51 |

Self-reported sedentary time (hours/day)

| Q1 | 7016 | 1.5 (1.0) | 336.23 <.0001 | 3.87 <.0001 | 0.98 <.0001 | 10.88 <.0001 | 63.53 <.0001 | 23.43 <.0001 |
| Q2 | 5971 | 3.0 (0.5) | 328.45 .1 | 3.84 .4 | 1.01 <.0001 | 11.47 <.0001 | 61.51 <.0001 | 23.23 <.0001 |
| Q3 | 3766 | 4.0 (0.5) | 330.28 | 3.90 | 1.02 | 11.79 | 60.32 | 23.09 |
| Q4 | 4005 | 6.0 (2.0) | 326.64 | 3.91 | 1.04 | 12.25 | 58.44 | 22.89 |

Adjusted for age, phase of menstrual cycle, ethnicity, time since last birth, time since last oral contraceptive pill use, smoking, alcohol, diet (fruit and vegetable, meat and fish, bread and cereal and spread type), Townsend deprivation index and region.

*aAdult BMI.
| Townsend deprivation index and region.

bAdult height.
FIGURE 1  Adjusted geometric means of serum hormones and SHBG by BMI and self-reported and accelerometer-measured physical activity in premenopausal women. *$P_{trend}$ adjusted for age, phase of menstrual cycle, ethnicity, time since last birth, time since last oral contraceptive pill use, smoking, alcohol, diet (fruit and vegetable, meat and fish, bread and cereal and spread type), Townsend deprivation index and region. **$P_{trend}$ adjusted as above and for BMI. Error bars represent the 95% confidence interval of a geometric mean.
The exposure-outcome associations are described below only if there was at least a 5% difference in hormone concentrations between the highest and lowest exposure groups.

3.1 Premenopausal women

3.1.1 Body size and composition

Women with a higher BMI had lower concentrations of total oestradiol, SHBG and IGF-I (15%, 51% and 14% difference respectively in the highest vs lowest BMI group) and higher concentrations of calculated free oestradiol and total and calculated free testosterone (22%, 29% and 113% difference respectively; Table 2 and Figure 1). Similar associations were observed in women with a higher waist to height ratio, a higher waist to hip ratio or higher body or trunk fat mass (Table 2). Taller women had a 6% lower concentration of calculated free testosterone. After additional adjustment for BMI, the associations with other anthropometric measures were attenuated and became insignificant for calculated free oestradiol, total testosterone and IGF-I (Table S1).

Comparative body size at Age 10 was also associated with certain hormone concentrations (Table 2). After adjustment for adult BMI, women who were plumper at Age 10 had an 10% lower concentration of calculated free testosterone and a 10% higher concentration of SHBG, compared to those who were thinner at Age 10 (Table S1).

3.1.2 Physical activity and sedentary time

More active women had a lower concentration of calculated free testosterone (10% difference in the most vs least active group) and a
higher concentration of SHBG (11% difference; Table 2 and Figure 1). The associations were more pronounced with accelerometer-measured physical activity; more active women also had a lower concentration of total testosterone. More sedentary time was associated with higher concentrations of total and calculated free testosterone (6% and 13% difference respectively in the most vs least sedentary group) and a lower concentration of SHBG (8% difference). These associations were attenuated after further adjustment for BMI (Figure 1 and Table S1). As there was no significant interaction of physical activity and sedentary time with BMI, in terms of their association with hormone levels, subgroup analyses by BMI were not presented.

3.1.3 | Subgroup analyses by phase of the menstrual cycle

The association with BMI was stronger for total oestradiol in the follicular phase and for calculated free oestradiol in the luteal phase (\(P_{\text{interaction}}\) between three BMI categories and six menstrual cycle phases = .0008 for total oestradiol and .0001 for calculated free oestradiol; Figure 2); similar findings were observed for other anthropometric measures but there was no strong evidence of variation in the associations of physical activity or sedentary time by cycle phase (Tables S3 and S4). The associations between BMI and other hormones and SHBG varied little by phase of the menstrual cycle (Figure 2).

Similar findings were observed when the sample was restricted to 10 024 women aged under 45 years (Table S5).

3.2 | Postmenopausal women

3.2.1 | Body size and composition

Obese women had higher concentrations of total and calculated free testosterone (39% and 126% difference respectively in the highest vs lowest BMI group), and lower concentrations of SHBG and IGF-I (51% and 12% difference, respectively; Table 3 and Figure 3). The associations were similar for other anthropometric measures except for height, but were attenuated after further adjustment for BMI (Table 3 and Table S2).

After adjustment for adult BMI, women who were plumper at Age 10 had a 14% lower concentration of calculated free testosterone and a 15% higher concentration of SHBG, compared to those who were thinner at Age 10 (Table S2).

3.2.2 | Physical activity and sedentary time

More active women had lower concentrations of total and calculated free testosterone (5% and 11% difference respectively in the most vs least active group) and a higher concentration of SHBG (10% difference; Table 3 and Figure 3). These associations were stronger with accelerometer-measured physical activity. More sedentary time was associated with higher concentrations of total and calculated free testosterone (6% and 15% difference respectively in the most vs least sedentary group) and a lower concentration of SHBG (11% difference). These associations were attenuated after further adjustment for BMI (Figure 3 and Table S2).

4 | DISCUSSION

In our study involving 20 758 premenopausal and 71 101 postmenopausal women, there were significant associations between body size and composition, physical activity and sedentary time and serum concentrations of hormones and SHBG, with the strongest associations observed for adult anthropometric factors.

4.1 | Total and calculated free oestradiol in premenopausal women

4.1.1 | Body size and composition

All the adult anthropometric factors measured in our study, except for height, were strongly associated with serum oestriadiol concentrations. The associations were negative for total oestradiol but were positive for calculated free oestradiol. The latter may have been driven by a lower concentration of SHBG in obese women; if calculated free oestradiol is a reliable index of bioavailable oestradiol that provides the oestrogenic stimulus to the tissues, our findings suggest a more oestrogenic environment in obese premenopausal women, but these relationships are not yet fully understood. Nevertheless, our findings confirm the results of previous smaller studies.

In the collaborative reanalysis of individual participant data from seven prospective studies, BMI in the 1699 control women was negatively associated with total oestradiol and positively associated with calculated free oestradiol. Similar findings have been reported in two US studies. A negative association with total oestradiol was also observed in the Nurses’ Health Study II although the association with calculated free oestradiol was not significant, and a Norwegian study found a positive association between BMI and measured free oestradiol.

The evidence regarding BMI and total oestradiol in non-white ethnic groups is less clear; a significant negative association was found in Japanese women whereas a significant positive association was observed in African American women.

In subgroup analyses by phase of the menstrual cycle, the negative association between BMI and total oestradiol was significant only in the follicular phase. Similar findings have been reported in other smaller studies, for example, from the US and Japan. Our analysis also showed that BMI was positively associated with calculated free oestradiol mainly in the luteal phase; this may be because total oestradiol did not vary by BMI in the luteal phase but SHBG was consistently lower in obese women throughout the menstrual cycle. A Norwegian study,
### TABLE 3  
Adjusted geometric means of serum hormones and SHBG in postmenopausal women

|                          | Total testosterone, nmol/L | Calculated free testosterone, pmol/L | SHBG, nmol/L | IGF, nmol/L |
|--------------------------|-----------------------------|--------------------------------------|--------------|-------------|
|                          | Geometric mean              |                                     | Geometric mean | Geometric mean |                                     | Geometric mean | Geometric mean | Geometric mean |
| n                        | Median (IQR)                |                                      | Geometric mean | Geometric mean |                                      | Geometric mean | Geometric mean | Geometric mean |
| **BMI (kg/m²)**          |                             |                                      |              |              |                                      |              |              |              |
| <22.5                    | 12 077                      | 21.3 (1.7)                           | 0.63         | <.0001       | 6.32                           | <.0001       | 72.87          | <.0001       | 19.83        | <.0001        |
| 22.5–24.9                | 16 661                      | 23.8 (1.2)                           | 0.69         | <.0001       | 7.80                           | <.0001       | 61.87          | <.0001       | 20.42        | <.0001        |
| 25.0–27.4                | 16 994                      | 26.1 (1.2)                           | 0.73         | 9.15         | 53.06                           | 20.30        |
| 27.5–29.9                | 11 134                      | 28.7 (1.2)                           | 0.76         | 10.44        | 46.59                           | 19.96        |
| 30.0–34.9                | 10 216                      | 31.9 (2.2)                           | 0.81         | 12.08        | 40.71                           | 19.03        |
| 35+                      | 4171                        | 37.6 (4.0)                           | 0.88         | 14.29        | 35.92                           | 17.41        |
| **Height (cm)**          |                             |                                      |              |              |                                      |              |              |              |
| Q1                       | 19 481                      | 155.2 (4.0)                          | 0.72         | <.0001       | 9.13                           | <.0001       | 52.40          | <.0001       | 19.55        | <.0001        |
| Q2                       | 17 771                      | 161.0 (2.0)                          | 0.73         | 9.11         | 53.02                           | <.0001       | 19.86          | <.0001        |
| Q3                       | 16 970                      | 164.0 (2.0)                          | 0.73         | 9.02         | 54.10                           | 19.91        |
| Q4                       | 17 031                      | 169.0 (4.0)                          | 0.72         | 8.84         | 54.75                           | 20.03        |
| **Waist to height ratio**|                             |                                      |              |              |                                      |              |              |              |
| Q1                       | 17 866                      | 0.44 (0.03)                          | 0.67         | <.0001       | 6.82                           | <.0001       | 71.22          | <.0001       | 20.07        | <.0001        |
| Q2                       | 17 799                      | 0.49 (0.02)                          | 0.71         | <.0001       | 8.41                           | <.0001       | 58.46          | <.0001       | 20.41        | <.0001        |
| Q3                       | 17 832                      | 0.53 (0.03)                          | 0.73         | 9.67         | 49.29                           | 20.10        |
| Q4                       | 17 756                      | 0.61 (0.06)                          | 0.79         | 11.99        | 39.90                           | 18.77        |
| **Waist to hip ratio**   |                             |                                      |              |              |                                      |              |              |              |
| Q1                       | 18 048                      | 0.74 (0.04)                          | 0.71         | <.0001       | 7.53                           | <.0001       | 67.49          | <.0001       | 19.96        | <.0001        |
| Q2                       | 17 591                      | 0.79 (0.02)                          | 0.72         | <.0001       | 8.63                           | <.0001       | 57.52          | <.0001       | 20.17        | <.0001        |
| Q3                       | 17 886                      | 0.84 (0.02)                          | 0.72         | 9.50         | 49.70                           | 19.96        |
| Q4                       | 17 728                      | 0.90 (0.05)                          | 0.74         | 10.79        | 42.38                           | 19.24        |
| **Body fat mass (kg)**   |                             |                                      |              |              |                                      |              |              |              |
| Q1                       | 17 981                      | 16.9 (4.0)                           | 0.65         | <.0001       | 6.77                           | <.0001       | 69.12          | <.0001       | 20.06        | <.0001        |
| Q2                       | 17 670                      | 22.6 (2.4)                           | 0.70         | <.0001       | 8.33                           | <.0001       | 57.70          | <.0001       | 20.38        | <.0001        |
| Q3                       | 17 825                      | 27.8 (3.1)                           | 0.75         | 9.76         | 49.95                           | 20.08        |
| Q4                       | 17 777                      | 36.8 (8.4)                           | 0.81         | 12.09        | 41.09                           | 18.83        |
| **Trunk fat mass (kg)**  |                             |                                      |              |              |                                      |              |              |              |
| Q1                       | 18 200                      | 8.2 (2.4)                            | 0.65         | <.0001       | 6.93                           | <.0001       | 67.74          | <.0001       | 20.11        | <.0001        |
| Q2                       | 17 844                      | 11.5 (1.4)                           | 0.70         | <.0001       | 8.43                           | <.0001       | 57.02          | <.0001       | 20.33        | <.0001        |
| Q3                       | 17 553                      | 14.5 (1.7)                           | 0.74         | 9.72         | 50.11                           | 20.04        |
| Q4                       | 17 656                      | 19.2 (4.1)                           | 0.80         | 11.81        | 42.04                           | 18.85        |
| **Comparable body size at age 10** |                     |                                      |              |              |                                      |              |              |              |
| Thinner                  | 22 001                      | 25.3 (5.3)                           | 0.72         | <.0001       | 9.21                           | <.0001       | 52.03          | <.0001       | 19.98        | <.0001        |
| About average            | 37 204                      | 25.8 (5.4)                           | 0.72         | 8.88         | 54.68                           | .01          | 19.90          | <.0001        |
| Plumper                  | 12 048                      | 27.9 (6.8)                           | 0.73         | 9.19         | 52.72                           | 19.33        |
| **Comparable height at age 10** |                     |                                      |              |              |                                      |              |              |              |
| Shorter                  | 15 045                      | 156.0 (6.5)                          | 0.71         | <.0001       | 8.92                           | <.0001       | 53.18          | <.0001       | 19.57        | <.0001        |
| About average            | 38 231                      | 162.0 (6.0)                          | 0.72         | 9.01         | 53.65                           | .2           | 19.82          | <.0001        |
| Taller                   | 17 977                      | 168.0 (7.0)                          | 0.73         | 9.17         | 53.51                           | 20.07        |
| **Self-reported physical activity (MET-hours/week)** |                     |                                      |              |              |                                      |              |              |              |
| Q1                       | 17 814                      | 7.9 (6.9)                            | 0.74         | <.0001       | 9.60                           | <.0001       | 50.63          | <.0001       | 19.66        | <.0001        |
however, found a significant positive association between BMI and measured free oestradiol in both follicular and luteal phases.\textsuperscript{29}

Overall, our study confirms an inverse association of BMI with total oestradiol in the follicular phase, and possibly a positive association with calculated free oestradiol in the luteal phase. The former may explain why the risk of breast cancer is lower in obese premenopausal women\textsuperscript{33} since follicular phase oestrogen has been shown to influence breast cancer risk.\textsuperscript{34} However, given the higher level of mitosis in the breast tissue during the luteal phase\textsuperscript{18} and the higher concentration of free oestradiol in obese women during this phase, it is likely that other hormones not measured in our study, for example progesterone, may also play a role in reducing the breast cancer risk in obese premenopausal women.\textsuperscript{35}

\subsection*{4.1.2 | Physical activity and sedentary time}

We did not find a significant association of self-reported or accelerometer-measured physical activity with total oestradiol. More active women seemed to have a lower concentration of calculated free oestradiol but the difference was small. Self-reported sedentary time was also not associated with total or calculated free oestradiol. Likewise, an analysis in the EPIC study found no significant association between self-reported physical activity and total or calculated free oestradiol\textsuperscript{36} although in a separate dataset from EPIC-Oxford there was an inverse association of total oestradiol with vigorous physical activity.\textsuperscript{37}

A small number of randomised trials have assessed the effects of exercise on oestradiol concentrations in premenopausal women but the results are mixed.\textsuperscript{15} The largest trial involving 391 US women reported no significant effect of an aerobic exercise intervention on total or calculated free oestradiol.\textsuperscript{38}

Overall, the evidence to date shows that the associations of physical activity and sedentary time with oestradiol concentrations are at most modest, and may not explain the effects of these lifestyle factors on cancer risk.

\subsection*{4.2 | Total and calculated free testosterone in premenopausal and postmenopausal women}

\subsubsection*{4.2.1 | Body size and composition}

We found that BMI was positively associated with total and calculated free testosterone in both premenopausal and postmenopausal women. This may be due to obesity-related changes in insulin and its effect on the ovarian regulatory system.\textsuperscript{29} The association with calculated free testosterone was stronger, reflecting a lower concentration of SHBG in obese women. Similar findings have been reported in several smaller studies.\textsuperscript{17,28,30,40}

We found that comparative body size at Age 10 was negatively associated with calculated free testosterone particularly after adjustment for adult BMI. The Nurses’ Health Study II involving 592 premenopausal women, however, did not find a significant...
Overall, our study confirms that adult BMI is positively associated with total and calculated free testosterone in both premenopausal and postmenopausal women; this may contribute to a higher risk of cancer, except premenopausal breast cancer, in obese women. The negative association between childhood body size and free testosterone is weak.

### 4.2.2 Physical activity and sedentary time

In our study, physical activity was negatively associated with testosterone concentrations, and the opposite was true for sedentary time. The associations were attenuated after adjustment for BMI. The results from previous smaller studies, however, varied widely; some found a significant negative association with total and/or free testosterone, but others reported no significant associations.
A meta-analysis of randomised controlled trials showed a significant decrease in free testosterone (mean difference = −0.62 [95% CI: −1.01, −0.24] pmol/L; nine trials) after exercise interventions, but no significant change in total testosterone.15

Overall, our study shows that physical activity is negatively associated with testosterone concentrations in both premenopausal and postmenopausal women but the effect size is small compared to that of BMI.

4.3 | SHBG in premenopausal and postmenopausal women

4.3.1 | Body size and composition

We found a strong negative association between BMI and SHBG concentrations. Similar associations have been reported in many other studies.17,26,28,30,37,40 The observed association may be due to the increased insulin level46 and changes in pro-inflammatory and anti-inflammatory cytokines47 in obese women, which downregulate hepatic synthesis of SHBG.

Women who were plumper at Age 10 had a slightly higher concentration of SHBG. In contrast, there was no significant association between childhood body shape and adult SHBG in the Nurses’ Health Study II.28

Overall, our study confirms a strong negative association between adult BMI and SHBG, which may partly explain why the risk of several cancers, except premenopausal breast cancer, is higher in obese women. The positive association between childhood body size and SHBG is weak.

4.3.2 | Physical activity and sedentary time

In this cohort, physical activity was positively associated with and sedentary time was negatively associated with SHBG concentrations. The associations were much weaker after adjustment for BMI. Similarly, the EPIC-Norfolk study reported a weak positive association between physical activity and SHBG in 2082 postmenopausal women43 whereas other smaller studies reported no significant association especially after adjustment for BMI.36,37,41,42,45 A previous meta-analysis showed a significant increase in SHBG after exercise interventions but the effect seemed to be confined to women with polycystic ovary syndrome.15

Overall, our study shows that the associations of physical activity and sedentary time with the SHBG concentration are modest, particularly after adjustment for BMI.

4.4 | IGF-I in premenopausal and postmenopausal women

4.4.1 | Body size and composition

Our analysis showed that the association between BMI and IGF-I was nonlinear as reported in previous studies40,48; the lowest concentration of IGF-I was observed in the highest BMI group. This may be related to the reduced growth hormone secretion caused by the increased insulin level in these women.49

Overall, our study confirms a nonlinear inverse association between BMI and IGF-I, which may partly contribute to a lower risk of breast cancer in obese premenopausal women. A pooled individual data analysis of 17 prospective studies associated high concentrations of IGF-I with an increased risk of breast cancer.12

4.4.2 | Physical activity and sedentary time

In our cohort, physical activity was positively associated with IGF-I concentrations and the opposite was true for sedentary time. The effect sizes were, however, very small and after adjustment for BMI, only the association with sedentary time in premenopausal women remained significant. Likewise, many studies reported nonsignificant findings14,36,41 although some found a positive association.50

Overall, our study confirms that the associations of physical activity and sedentary time with the IGF-I concentration are negligible, particularly after adjustment for BMI.

4.5 | Strengths and limitations

The notable strengths of our study are the very large sample size, availability of objectively measured exposures (physical activity and body size and composition) and detailed information on a wide range of potential confounders. Limitations include the cross-sectional design, use of accelerometer data collected on average 5 years after baseline assessment, use of self-reported sedentary time, use of blood samples collected at a single point in time and the lack of data on oestrogen concentrations in postmenopausal women and on other hormones such as progesterone and androgens other than testosterone.

4.6 | Summary and conclusions

In summary, obese premenopausal women had a lower concentration of total oestradiol and a higher concentration of calculated free oestradiol. Obese women also had higher concentrations of total and calculated free testosterone and lower concentrations of SHBG and IGF-I; these associations were similar in premenopausal and postmenopausal women.

More active premenopausal and postmenopausal women also had lower concentrations of total and free testosterone and a higher concentration of SHBG; the opposite was true for more sedentary women. The effect sizes of physical activity and sedentary time were, however, very small compared to those of BMI.

To conclude, our study confirms strong associations between adult anthropometric factors and hormone and SHBG concentrations in both premenopausal and postmenopausal women; this may partly
explain the effects of these factors on cancer risks. The associations with physical activity and sedentary time were at most modest.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest.

DATA ACCESSIBILITY
UK Biobank is an open access resource, and the study website https://www.ukbiobank.ac.uk/ has information on available data and access procedures.

ETHICAL APPROVAL
This research is covered by the approval of the UK Biobank research ethics committee (approval number 11/NW/0382).

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SUPPORTING INFORMATION

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