Title

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Journal

Cancer Epidemiology Biomarkers & Prevention, 31(1)

ISSN

1055-9965

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Publication Date

2022

DOI

10.1158/1055-9965.epi-21-0809

Peer reviewed

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2022 January ; 31(1): 97–107. doi:10.1158/1055-9965.EPI-21-0809.

Recreational physical activity, sitting, and androgen metabolism among postmenopausal women in the Women's Health Initiative Observational Study

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Authors' contributions:

HO performed the statistical analyses and drafted the manuscript. BT developed and designed the study and made substantial contributions to statistical analysis, interpretation of data, and critical revision and editing of the manuscript. XX developed and performed the assay and contributed to revision of the manuscript. GLA, HO-B, RP, PR, AHS, NS, LU, and RAW made substantial contributions to interpretation of data and revision of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Completing interests

Authors declare no conflict of interest.

Ethical Approval and Consent to participate

The Office of Human Subjects Research at the National Institutes of Health approved this analysis. As required by the WHI protocol, informed consent was obtained from all study subjects. Informed consent documents and procedures were approved by the Institutional Review Board (IRB) of the Fred Hutchinson Cancer Research Center, and by the IRBs of each of the participating clinical centers.

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Abstract

Background: Prolonged sitting and physical inactivity are associated with higher circulating levels of estrogens. It is unknown whether these risk factors are associated with circulating androgens/androgen metabolites, another set of hormones implicated in the etiology of cancers in postmenopausal women.

Methods: We conducted a cross-sectional analysis of 1,782 postmenopausal women in the Women's Health Initiative Observational Study. Serum concentrations of 12 androgens/androgen metabolites were quantified using liquid chromatography-tandem mass spectrometry. Physical activity and sitting time were self-reported at baseline. We performed linear regression to estimate geometric means (GMs) of androgen/androgen metabolite concentrations (pmol/L) according to physical activity and sitting time, adjusting for potential confounders and stratified by menopausal hormone therapy (MHT) use.

Results: Physical activity (≥15 vs. 0 MET-hour/week) was inversely associated with estrogen-to-androgen ratios among never/former MHT users (adj-GM=37.5 vs. 49.6 unconjugated estrone:androstenedione; 20.2 vs. 30.3 unconjugated estradiol:testosterone; all p-trend≤0.03) but was not associated among current MHT users. Prolonged sitting (≥10 vs. ≤5 hours/day) was positively associated with these ratios among both never/former (adj-GM=44.2 vs. 38.3, p-trend=0.10; adj-GM=23.4 vs. 20.2, p-trend=0.17; respectively) and current MHT users (adj-GM=197 vs. 147; 105 vs. 75.5; respectively; all p-trend≤0.02) but the associations were statistically significant among current MHT users only. The associations persisted after adjustment for BMI. After adjustment for adrenal androgens, physical activity and sitting were not associated with androgen metabolites.

Conclusions: Physical activity and sitting were associated with serum estrogen-to-androgen ratios but not androgen metabolites.

Impact: This study contributes to our understanding of the link between physical activity, sitting, and cancer risk in postmenopausal women.

Keywords

Sitting; sedentary; physical activity; exercise; androgen; estrogen; AM; sex steroid hormones; hormone metabolites; postmenopausal; hormone metabolism

INTRODUCTION

Synthesis and metabolism of sex steroid hormones including estrogens and androgens are believed to be a key mechanism that is involved in breast (1–3), endometrial (4,5), and ovarian carcinogenesis (6–14). Some studies have suggested that risk factors including prolonged sitting and physical inactivity can alter sex steroid hormone synthesis and metabolism in postmenopausal women. In randomized controlled trials, serum levels of estrogens (estrone, estradiol) (15–17) and testosterone (16,18) were reduced in postmenopausal women who exercised. In the Women's Health Initiative Observational

Study (WHI-OS), we previously reported that both prolonged sitting and physical inactivity were independently associated with elevated serum levels of estrone and estradiol among never/former menopausal hormone therapy (MHT) users (19). With prolonged sitting, similar positive associations with estrogens were found among current MHT users (19). Studies suggest that prolonged sitting and physical inactivity may influence estrogen production by increasing aromatization of androgens (20,21). Prolonged sitting and physical inactivity are also associated with increased body fat, a primary site of peripheral aromatization in postmenopausal women (22). Further, when estrogen metabolites were evaluated, prolonged sitting was also associated with metabolism of estrogens, particularly methylated catechol estrogen metabolites, the estrogen metabolites implicated in breast carcinogenesis (19). However, it is unknown whether prolonged sitting and physical inactivity are also associated with metabolism of androgens.

In postmenopausal women, androgens may increase cancer risk (e.g., breast, ovarian, endometrial) (1,4,6–13) directly via androgen signaling that increases cellular proliferation (23–25) and indirectly through aromatization to estrogens (21). Androgens may also influence immune system (26) and microenvironment of pre-cancerous cells. Androgen metabolism profiles reflect the levels of androgen production, metabolism, clearance, and enterohepatic recycling that are relevant to cancer risk. Metabolism of androgens occurs in peripheral target tissues (27), forming downstream metabolites: 5α-reduced metabolites and 5β-reduced metabolites. Studies suggest that individual androgen metabolites have varying carcinogenic properties (28,29). For example, 5α-reduced metabolites, particularly dihydrotestosterone (DHT), are known to be the most potent bioactive metabolites, while its sulfated form, dihydrotestosterone sulfate (DHTS), may serve as an inactive reservoir. Studies also suggest DHT does not adequately reflect 5α-reductase activity, and instead 5α-reduced glucuronide metabolites (androsterone-glucuronide [ADT-G], 5α-androstane-3α,17β diol-3-glucuronide [3α-diol-3G], 5α-androstane-3α,17β diol-17-glucuronide [3α-diol-17G]) together may be a better indicator of tissue-level androgenicity (27,30). In this study, we examined associations of recreational physical activity and sitting time with 12 serum androgens/androgen metabolites among postmenopausal women in the WHI-OS. Understanding associations between known risk factors and detailed androgen metabolism profiles may illuminate mechanisms through which these risk factors affect cancer risk.

MATERIALS AND METHODS

Study population

In the WHO-OS, we conducted a cross-sectional analysis using baseline data from participants of a nested case-control study of ovarian and endometrial cancers(5,14). The WHI-OS is an ongoing cohort study of 93,676 postmenopausal women (aged 50–79 years) who were recruited from 40 US clinical centers in 1993–1998 (31,32). At the baseline clinical visit, body weight, height, and waist and hip circumferences were measured, and blood samples were collected. Baseline questionnaires collected information on demographic characteristics and lifestyle factors including physical activity and sitting time.

Details of the nested case-control study are described elsewhere (5,14). In brief, cases were women with ovarian or endometrial cancer diagnosed between baseline and 2012. For each case, controls were selected among women who remained free of cancer at the date the case was diagnosed (index date), matched to the case based on age at baseline, year of blood draw, self-identified race and ethnicity, hysterectomy at baseline or during follow-up prior to the index date (for ovarian controls only), and MHT use. Both cases and controls had no history of cancer (except non-melanoma skin cancer), bilateral oophorectomy, or hysterectomy (for endometrial controls only), and had ≥1.1 mL serum available.

Among 1,824 participating women, we excluded women who had missing information on physical activity or sitting time variables (n=31) and had missing values for at least one androgens/androgen metabolite (n=11). After exclusion, a total of 1,782 women (486 cases and 442 controls among never/former MHT users, 447 cases and 407 controls among current MHT users), representing 54,511 women when weighted back to the entire cohort, were included in this analysis. Because all serum samples were collected at baseline prior to any cancer diagnosis, we included both cases and controls in the analysis and accounted for case-control selection criteria using inverse probability sampling weights.

Written informed consent was obtained from all study participants. All procedures were conducted in accordance with the Declaration of Helsinki. All procedures were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center (WHI Clinical Coordinating Center), as well as each participating clinical centers, and the Office of Human Subjects Research at the National Institute of Health.

Exposure assessment

Time spent sitting and levels of recreational physical activity were assessed via self-administered baseline questionnaire. Sitting time (e.g., sitting at work, sitting while eating, driving, riding in a car or bus, or watching TV) during a usual day was reported in one of eight categories (<4, 4–5, 6–7, 8–9, 10–11, 12–13, 14–15, ≥16 hours/day). We combined the categories into three groups (≤5, 6–9, ≥10 hours/day) to ensure sufficient sample sizes in all groups. Usual exercise or recreational physical activity was reported in number of days per week (1, 2, 3, 4, ≥5) and minutes per session (<20, 20–39, 40–59, ≥60) spent on moderate-intensity exercise, vigorous-intensity exercise, and walking outside the home (average-paced, fairly fast, very fast), separately. We calculated the total metabolic equivalent (MET)-hour/week of moderate- to vigorous-intensity activity (including walking) by multiplying the summed number of hours per week of each activity type with its corresponding average MET values (33). Based on the Physical Activity Guidelines for Americans, we categorized participants into four groups (0 [no exercise], 0.1–7.4 [not meeting the guideline], 7.5–14.9 [meeting the guideline], ≥15.0 MET-hour/wk [exceeding the guideline]).

Laboratory assays

We measured the concentrations of androgens/androgen metabolites in serum samples collected at baseline. Details of the assay methods are described elsewhere (13). Briefly, the assay quantified the serum concentrations of 12 individual androgens/

androgen metabolites including four adrenal androgens (dehydroepiandrosterone [DHEA], dehydroepiandrosterone sulfate [DHEAS], androstenedione, testosterone), seven 5α-reduced metabolites (5α-androstanedione, DHT, DHTS, androsterone [ADT], ADT-G, 3α-diol-3G, 3α-diol-17G]), and one 5β-reduced metabolite (etiocholanolone-glucuronide [Etio-G]) using a stable isotope dilution high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Thermo Fisher, San Jose, CA; Shimadzu Scientific Instruments, Columbia, MD) (34). We included only one 5β-reduced metabolite (Etio-G) because other 5β-reduced metabolites were very low in serum concentrations, did not have internal standards, or bind very weakly to the androgen receptor. Because studies suggest circulating levels of 5α-reduced glucuronide metabolites may better reflect total androgenicity than their precursors (27,30), we summed the concentrations of ADT-G, 3α-diol-3G, and 3α-diol-17G to use as a surrogate marker of tissue-level androgenic activity. Serum concentrations of estrogens (estradiol and estrone) were previously quantified using an independent LC-MS/MS assay (5,35). Using the measures on individual androgens/androgen metabolites and estrogens, we calculated four different ratios (DHEAS:DHEA, DHTS:DHT, unconjugated estrone:androstenedione, unconjugated estradiol:testosterone). Estrogen-to-androgen ratios (unconjugated estrone:androstenedione, unconjugated estradiol:testosterone) indicate the extent of aromatase activity (conversion of androstenedione and testosterone into estrone and estradiol, respectively). Coefficients of variation (CVs) of the assay were <11% and intraclass correlation coefficients (ICCs) ranged from 0.77 to 0.997 (13).

Statistical analyses

Because the concentrations of androgens/androgen metabolites and estrogens vary by MHT use, we stratified all analyses by MHT use (n=928 never/former vs. n=854 current users). Using methods for secondary phenotype analysis of case-control data described by Li and Gail (36), all analyses were weighted by inverse probability sampling weights to adjust the data to represent the population in the entire cohort. The sampling fractions were 1 for all cases and varied for controls depending on their strata defined by matching factors. To improve normality of the residuals, we log-transformed androgens/androgen metabolite data. Inverse probability weighted multivariable linear regression models were used to estimate geometric means (GMs) and 95% confidence intervals (CIs) of androgens/androgen metabolite concentrations (pmol/L) and related ratios according to exposure categories (physical activity, sitting time), adjusting for potential confounders. Multivariable models included age at blood draw, calendar year at blood draw, race (a proxy for body composition and socioeconomic factors that may influence lifestyle and hormone levels), smoking status, alcohol drinking, parity, family history of breast or ovarian cancer, and time since menopause. Among never/former MHT users, we additionally included MHT use (never vs. former) in the multivariable models. Because adiposity plays an important role in altering sex hormone synthesis and metabolism (e.g., aromatization of androgens) (37), we compared the models with and without adjustment for BMI and waist-to-hip ratio (WHR) to examine the associations independent of adiposity. For the analysis of androgen metabolites, we additionally adjusted for summed concentrations of adrenal androgens because the exposure associations with androgen metabolites can be driven by their associations with adrenal androgens, which serve as precursors for downstream

androgen metabolites. The percent change in GMs from the lowest to highest exposure categories was estimated by taking the ratio of GM difference between the two categories over the GM of the lowest category, multiplied by 100. We tested for linear trend using Wald tests for continuous exposure variables. We also performed restricted cubic spline models to assess for nonlinearity of the associations, but the model fit was not statistically significantly better than linear models. For this reason, we presented results from linear models only. To examine whether the associations vary by BMI, we also stratified the analyses by current BMI (≥30 kg/m^2 [obese] vs. <30 kg/m^2 [nonobese]) and tested for interaction using Wald test for product terms.

In secondary analysis, we further investigated the relationships with aromatization by comparing the mean proportions of adrenal androgens (DHEA, DHEAS, androstenedione, testosterone) out of summed concentrations of adrenal androgens and estrogens (estrone and estradiol) across exposure categories, with adjustment for the summed concentration of adrenal androgens and estrogens. Because adrenal androgens are converted to estrogens during aromatization, the proportion of adrenal androgens should decrease while the proportion of estrogens increase in the setting of elevated aromatization.

All statistical tests were two-sided with a 5% type I error rate. Bonferroni correction was performed to account for multiple comparisons (17 tests per exposure). Analyses were conducted using SURVEY procedures in SAS version 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Study population characteristics

The mean age was 64.6 years in never/former MHT users and 61.3 years in current MHT users. Levels of physical activity and sitting time were only weakly correlated among both never/former (Spearman r= −0.08, p=0.02) and current MHT users (Spearman r= −0.13, p<0.001). Participant characteristics by physical activity and sitting time are presented in Table 1 for never/former MHT users and Supplementary Table 1 for current MHT users. Among both never/former and current MHT users, participants with higher levels of physical activity (≥15 vs. 0 MET-hour/wk) were less likely to be obese (Table 1). Participants with prolonged sitting (≥10 vs. ≤5 hours/day) were more likely to be younger, obese, and have family history of breast or ovarian cancer.

Recreational physical activity

Among never/former MHT users, higher levels of recreational physical activity (≥15 vs. 0 MET-hour/week) were associated with lower levels of estrogen-to-androgen ratios (GM=37.5 vs. 49.6 unconjugated estrone:androstenedione; 20.2 vs. 30.3 unconjugated estradiol:testosterone; all p-trend≤0.03) (Table 2). After adjustment for BMI, these differences were substantially attenuated (GM=40.8 vs. 47.7, p-trend=0.20 for unconjugated estrone:androstenedione; GM=24.8 vs. 27.6, p-trend=0.91 for unconjugated estradiol:testosterone) and no longer statistically significant. Physical activity was not associated with serum concentrations of adrenal androgens among never/former MHT users.

Among current MHT users, higher levels of physical activity were associated with slightly lower serum adrenal androgens (GM=3.75 vs. 4.37 pmol/L, p-trend=0.02 for DHEA; 845 vs. 1022 pmol/L, p-trend=0.04 for DHEAS; 1.17 vs. 1.32 pmol/L, p-trend=0.10 for androstenedione). The associations were attenuated after adjustment for BMI.

In secondary analysis, there was no association between physical activity and the proportion of adrenal androgens out of summed concentrations of adrenal androgens and estrogens (Supplementary Table 2).

Table 3 presents the associations between recreational physical activity and serum androgen metabolites, adjusting for BMI. Among never/former MHT users, recreational physical activity (≥15 vs. 0 MET-hour/week) was not associated with androgen metabolites. Among current MHT users, physical activity was associated with lower serum concentrations of 5α-reduced glucuronide metabolites (GM=14.3 vs. 16.3 pmol/L, p-trend=0.30 for ADT-G; 1.13 vs. 1.32 pmol/L, p-trend=0.13 for 3α-diol-3G; 0.70 vs. 0.84 pmol/L, p-trend=0.02 for 3α-diol-17G) and 5β-reduced metabolites (30.2 vs. 36.3 pmol/L, p-trend=0.16 for Etio-G). However, there was no association with 5α-reduced glucuronide metabolites and 5β-reduced metabolites after additional adjustment for adrenal androgens (precursors for androgen metabolites).

Sitting time

Among never/former MHT users, prolonged sitting (≥10 vs. ≤5 hours/day) was associated with slightly higher serum concentrations of androstenedione (GM=1.53 vs. 1.38 pmol/L, p-trend=0.11) and estrogen-to-androgen ratios (GM=44.2 vs. 38.3, p-trend=0.10 for unconjugated estrone:androstenedione; 23.4 vs. 20.2, p-trend=0.17 for unconjugated estradiol:testosterone; Table 4); however, these associations were not statistical significant. Among current MHT users, the positive associations between prolonged sitting and estrogen-to-androgen ratios were also observed (GM=197 vs. 147 unconjugated estrone:androstenedione; 105 vs. 75.5 unconjugated estradiol:testosterone; all p-trend≤0.02) and the associations were statistically significant. Prolonged sitting was not associated with serum adrenal androgens in current MHT users. Among both never/former and current MHT users, the associations did not change after additional adjustment for BMI.

In secondary analysis, women with prolonged sitting had slightly lower proportion of adrenal androgens out of summed concentrations of adrenal androgens and estrogens among both never/former (68.6% vs. 70.5%, p=0.73) and current MHT users (26.2% vs. 29.7%, p=0.06; Supplementary Table 2).

After adjustment for BMI, prolonged sitting (≥10 vs. ≤5 hours/day) was not associated with serum androgen metabolites in never/former MHT users, while in current MHT users, an inverse association with 5α-androstanedione (GM=1.20 vs. 1.39 pmol/L, p-trend=0.05) was observed (Table 5). Additional adjustment for adrenal androgens did not change the results.

Similar results were observed with adjustment for WHR, instead of BMI (Supplementary Table 3–6). When stratified by BMI, the associations were not significantly different between obese vs. nonobese women (p-interaction>0.05; Supplementary Table 7–10).

After Bonferroni correction for multiple comparisons, none of the associations remained statistically significant.

DISCUSSION

In this cross-sectional analysis of detailed serum androgen metabolism, we observed statistically significant inverse associations between recreational physical activity and estrogen-to-androgen ratios among never/former MHT users and positive associations between prolonged sitting and estrogen-to-androgen ratios among current MHT users. Among both never/former and current MHT users, physical activity and prolonged sitting were not associated with serum androgen metabolites after adjustment for adrenal androgens. Our data suggest that physical activity and sitting may not be associated with the metabolism of adrenal androgens beyond aromatization to estrogens in postmenopausal women.

Our finding of inverse associations between physical activity and serum estrogen-to-androgen ratios among never/former MHT users are consistent with those from previous studies of estrogens. Studies (15–17,38–40), including our previous analysis in the WHI-OS (19), consistently reported lower levels of circulating estrone and estradiol associated with physical activity in postmenopausal women not using MHT. These inverse associations of physical activity with estrogen-to-androgen ratios are likely to be primarily driven by the reduced estrogen levels in active women because in the present study we observed similar serum concentrations of adrenal androgens between women who were active vs. not active. We also observed that the inverse associations with estrogen-to-androgen ratios were substantially attenuated after adjustment for BMI or WHR. Our findings suggest that physical activity may be associated with estrogen-to-androgen ratios possibly by reducing adipose tissue. Because adipose tissues can convert androgens to estrogens via aromatase activity, reduced body fat in active women may lead to declined aromatization of androgens and reduced circulating levels of estrogens. However, in our cross-sectional data, BMI may also play as a confounder, influencing physical activity and sitting behaviors, and thus further studies are needed to evaluate the mediating effects of BMI using longitudinal studies. It is also possible that aromatization-independent pathways influence serum estrogen-to-androgen ratios. Although reduced aromatization of androgens in active women should lead to increased circulating levels of adrenal androgens (precursor substrates for estrogens), in the present study we did not observe higher serum concentrations of adrenal androgens in active women, suggesting that physical activity may also be associated with lower androgen production (or retention) balancing the levels of androgens. Consistently, among current MHT users, we observed slightly lower serum concentrations of adrenal androgens in active women, further supporting our notion that physical activity may reduce androgen production (or retention). The inverse associations with circulating adrenal androgens may appear stronger in current MHT users because aromatase activity, as well as circulating levels of estrogens, is not strongly associated with physical activity in current MHT users (19) possibly due to already-suppressed aromatization of androgens in the presence of excess estrogens. Because adipose tissues also contain 17β-hydroxysteroid dehydrogenase enzyme, which converts androstenedione to testosterone, lower body fat in active women may also contribute to reduction in testosterone production (41). Among

previous studies, physical activity was inversely associated with circulating levels of testosterone in some studies (16,18,38,39) but not associated in others (17). Further studies are needed to clarify the effects of physical activity on androgen production and retention in postmenopausal women.

In the present study, sitting was associated with higher estrogen-to-androgen ratios among postmenopausal women. Although the associations were statistically significant among current MHT users only, the direction of associations were consistent among both never/former and current MHT users. Prolonged sitting may influence circulating levels of estrogens and androgens by increasing body fat and replacing physically active time. In the present study, the positive associations with estrogen-to-androgen ratios persisted after additional adjustment for BMI, suggesting that the associations are independent of BMI. This finding is consistent with our previous report (19) of positive associations between prolonged sitting and serum estrogens after adjustment for BMI. In the present study, prolonged sitting was also suggestively associated with lower proportions of adrenal androgens out of summed concentrations of adrenal androgens and estrogens while holding the summed concentration constant and adjusting for BMI, indicating an increased replacement of androgens for estrogens (e.g., elevated aromatase activity).

To the best of our knowledge, this study is the first to investigate the associations of physical activity and sitting with detailed androgen metabolism beyond aromatization to estrogens. We observed no independent association of physical activity and sitting with serum androgen metabolites. The overall inverse associations between physical activity and androgen metabolites disappeared after additional adjustment for adrenal androgens, suggesting that the association were largely driven by the reduced total concentration of adrenal androgens (precursors for androgen metabolites). Our data suggest that physical activity and sitting may not strongly influence androgen metabolism beyond aromatization to estrogens. Given the cross-sectional design of study, further studies are needed to confirm our results using a longitudinal design.

This study has important strengths. Use of a high-performance LC-MS/MS assay allowed highly sensitive evaluation of serum androgens/androgen metabolites. We also increased the validity of our results by careful adjustment for potential confounders. We also acknowledge several limitations of this study. Given the cross-sectional design of the study, it is difficult to clarify the temporal relationships between physical activity, sitting, BMI, and androgens and thus the associations that we observed in the study may not be causal. Because excess androgens can also lead to weight gain and body fat accumulation (42), current BMI in our data may not reflect mediating effect in the relationships between physical activity and androgens. Physical activity and sitting data were also self-reported and thus may be prone to measurement errors. However, measurement errors are unlikely to be related to serum levels of androgens/androgen metabolites, and the WHI physical activity questionnaire has been shown to have a good test-retest reliability (ICC=0.77) (43). Physical activity data were also primarily focused on recreational activities and may not reflect other types of physical activity (e.g., occupational, household). Further studies may be needed to clarify the associations accounting for other types of physical activity. Further, we used a single serum sample collected at baseline. However, we confirmed that most androgens/androgen

metabolite concentrations were highly stable over two-year period. Due to lack of data, we were also not able to adjust for the presence of endocrine disorders (e.g., polycystic ovary syndrome, congenital adrenal hyperplasia) that may influence androgen concentrations and lifestyle. Lastly, we performed multiple comparisons. After Bonferroni correction for multiple comparisons (17 tests per exposure), none of the associations that we observed in the study remained statistically significant. As some of the associations that we observed in the study may be due to chance (e.g., false positives), our results should be interpreted with caution.

In summary, recreational physical activity and sitting time were associated with serum estrogen-to-androgen ratios but not androgen metabolites. Our data suggest that physical activity and sitting may not influence androgen metabolism beyond aromatization to estrogens in postmenopausal women. Using a prospective study design, further studies may be needed to clarify the mediating role of androgen synthesis and metabolism in the relationships of physical activity and sitting time with cancer risk among postmenopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT:

The WHI program is supported by contracts from the National Heart, Lung and Blood Institute, NIH (Program Office: Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller). The authors thank the WHI Clinical Coordinating Center (Fred Hutchinson Cancer Research Center, Seattle WA) and the WHI investigators (Garnet Anderson, Ross Prentice, Andrea LaCroix, Charles Kooperberg, JoAnn E. Manson, Barbara V. Howard, Marcia L. Stefanick, Rebecca Jackson, Cynthia A. Thomson, Jean Wactawski-Wende, Marian Limacher, Jennifer Robinson, Lewis Kuller, Sally Shumaker, Robert Brunner, Karen L. Margolis) for their dedication, and the study participants for making the program possible. A full list of WHI investigators can be found at https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf

FUNDING:

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. This study was also supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics of the National Cancer Institute (B. Trabert). H. Oh was supported by the National Research Foundation of Korea (NRF) grants (2019R1G1A1004227, 2019S1A3A2099973) and Korea University grant (K2104831).

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Table 1.

Characteristics of study population according to sitting time and recreational physical activity in postmenopausal women not using menopausal hormone therapy: the Women's Health Initiative Observational Study

Characteristics	Physical activity (MET-hour/week)				Sitting time (hour/day)		
	0	0.1–7.4	7.5–14.9	≥15.0	≤5	6–9	≥10
N	199	213	219	297	321	385	222
Weighted N [a]	6048	6701	7322	10185	11310	12158	6787
	N (weighted %)				N (weighted %)		
Menopausal hormone therapy use							
Never	140 (58.9)	149 (54.2)	134 (52.5)	201 (61.2)	201 (54.1)	279 (63.8)	144 (50.2)
Former	59 (41.1)	64 (45.8)	85 (47.5)	96 (38.8)	120 (45.9)	106 (36.2)	78 (49.8)
Age at baseline blood draw							
<55 years	15 (4.3)	12 (8.8)	19 (7.1)	33 (10.5)	16 (3.6)	36 (7.2)	27 (16.9)
55–59 years	48 (22.9)	42 (18.4)	25 (11.7)	60 (17.8)	57 (13.4)	63 (18.0)	55 (23.5)
60–64 years	52 (21.9)	50 (21.6)	52 (21.1)	65 (19.5)	71 (18.8)	92 (22.5)	56 (21.3)
65–69 years	36 (21.8)	52 (25.6)	51 (23.4)	57 (23.1)	71 (23.8)	91 (27.3)	34 (15.9)
70–74 years	32 (21.4)	42 (18.6)	41 (18.7)	51 (19.4)	72 (28.3)	65 (15.4)	29 (12.0)
75–79 years	16 (7.7)	15 (7.0)	31 (18.1)	31 (9.8)	34 (12.1)	38 (9.7)	21 (10.5)
Race							
White	162 (84.2)	180 (84.9)	199 (90.9)	277 (94.0)	280 (89.0)	338 (88.0)	200 (92.2)
Non-White (Black, Asian, American Indian, Other)	37 (15.8)	33 (15.1)	20 (9.1)	20 (6.0)	41 (11.0)	47 (12.0)	22 (7.8)
Calendar year at blood draw							
1993 – 1996	116 (57.0)	129 (62.2)	132 (57.7)	188 (66.1)	186 (53.1)	241 (67.3)	138 (64.5)
1997 – 1998	83 (43.0)	84 (37.8)	87 (42.3)	109 (33.9)	135 (46.9)	144 (32.7)	84 (35.5)
Smoking status							
Never	92 (46.5)	111 (52.4)	117 (51.8)	152 (50.6)	173 (56.7)	189 (48.5)	110 (43.6)
Former	90 (42.8)	81 (38.1)	86 (37.8)	132 (43.7)	124 (35.0)	169 (42.4)	96 (47.8)
Current	17 (10.6)	21 (9.5)	16 (10.4)	13 (5.7)	24 (8.4)	27 (9.1)	16 (8.6)
Alcohol drinking							
Non-drinker	66 (27.8)	66 (31.6)	69 (36.0)	67 (23.6)	87 (30.4)	112 (27.8)	69 (29.6)
<1 drink/week	78 (42.8)	67 (25.0)	57 (24.6)	95 (29.8)	98 (27.7)	133 (32.7)	66 (29.3)

Characteristics		Physical activity (MET-hour/week)				Sitting time (hour/day)		
		0	0.1–7.4	7.5–14.9	≥15.0	≤5	6–9	≥10
	1–6 drink/week	29 (13.7)	56 (30.4)	63 (25.9)	79 (24.7)	86 (24.2)	99 (26.8)	42 (18.8)
	≥7 drink/week	26 (15.7)	24 (13.0)	30 (13.4)	56 (21.9)	50 (17.6)	41 (12.6)	45 (22.3)
Parous		171 (85.7)	176 (86.2)	187 (85.2)	245 (82.8)	271 (84.9)	327 (85.8)	181 (82.4)
Family history of breast or ovarian cancer		41 (20.9)	38 (20.2)	41 (14.4)	65 (24.3)	54 (15.8)	79 (22.9)	52 (23.0)
Time since menopause								
	<10 years	63 (29.4)	61 (29.4)	60 (25.5)	109 (33.4)	95 (26.9)	115 (27.3)	83 (39.1)
	10–19 years	82 (41.9)	82 (34.8)	92 (38.9)	96 (33.8)	118 (33.8)	150 (41.2)	84 (34.1)
	≥20 years	43 (23.5)	66 (33.6)	57 (31.0)	78 (27.9)	99 (35.8)	103 (27.4)	42 (20.8)
	Missing	11 (5.2)	4 (2.1)	10 (4.6)	14 (4.9)	9 (3.5)	17 (4.1)	13 (6.0)
Current BMI								
	<25.0 kg/m^2	38 (25.9)	71 (42.0)	94 (44.6)	133 (54.4)	128 (45.4)	138 (39.5)	70 (47.9)
	25.0–29.9 kg/m^2	58 (27.9)	66 (30.1)	74 (39.0)	90 (27.2)	116 (37.7)	113 (29.3)	59 (22.1)
	≥30.0 kg/m^2	103 (46.3)	76 (27.9)	51 (16.5)	74 (18.4)	77 (17.0)	134 (31.2)	93 (30.0)

[a]Weighted N reflects weighted counts and refers to the study cohort

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Table 2.

Geometric means (pmol/L) and 95% confidence intervals (CI) of serum adrenal androgens and ratios by recreational physical activity in postmenopausal women, stratified by menopausal hormone therapy use: the Women's Health Initiative Observational Study

	Model 1[a]						Model 1 + BMI[b]					
	Recreational physical activity (MET-hour/week)						Recreational physical activity (MET-hour/week)					
	0	0.1–7.4	7.5–14.9	≥15.0	%Δ[c]	p-trend[d]	0	0.1–7.4	7.5–14.9	≥15.0	%Δ[c]	p-trend[d]
Never/former menopausal hormone therapy users												
Adrenal androgens												
DHEA	5.07 (4.38, 5.88)	4.27 (3.66, 4.99)	4.98 (4.34, 5.72)	5.13 (4.46, 5.89)	1.2	0.38	5.03 (4.34, 5.83)	4.32 (3.70, 5.05)	5.04 (4.38, 5.79)	5.22 (4.51, 6.03)	3.8	0.91
DHEAS	1148 (974, 1353)	940 (785, 1125)	1113 (949, 1305)	1105 (950, 1286)	−3.7	0.74	1123 (950, 1327)	968 (808, 1160)	1147 (973, 1352)	1160 (989, 1360)	3.3	0.91
Androstenedione	1.47 (1.31, 1.64)	1.29 (1.15, 1.45)	1.49 (1.34, 1.65)	1.46 (1.33, 1.61)	−0.7	0.40	1.46 (1.30, 1.63)	1.30 (1.16, 1.46)	1.50 (1.35, 1.66)	1.48 (1.34, 1.64)	1.4	0.91
Testosterone	0.58 (0.51, 0.66)	0.56 (0.49, 0.64)	0.58 (0.51, 0.66)	0.56 (0.48, 0.65)	−3.4	0.80	0.58 (0.51, 0.66)	0.56 (0.49, 0.65)	0.58 (0.51, 0.66)	0.57 (0.48, 0.66)	−1.7	0.91
Ratios												
DHEAS: DHEA	226 (201, 255)	220 (195, 248)	223 (200, 250)	216 (195, 239)	−4.4	0.52	223 (198, 252)	224 (199, 253)	228 (203, 255)	222 (200, 247)	−0.4	0.97
Unconjugated estrone: Androstenedione	49.6 (41.9, 58.6)	38.3 (33.9, 43.3)	41.6 (35.7, 48.5)	37.5 (32.7, 43.0)	−24.4	0.01	47.7 (40.7, 55.8)	40.4 (35.8, 45.5)	43.9 (37.8, 50.9)	40.8 (35.6, 46.8)	−14.5	0.20
Unconjugated estradiol: Testosterone	30.3 (23.9, 38.6)	18.5 (15.3, 22.3)	25.3 (20.3, 31.5)	20.2 (16.3, 25.0)	−33.3	0.03	27.6 (22.0, 34.5)	21.0 (17.8, 24.8)	28.8 (23.5, 35.4)	24.8 (20.4, 30.1)	−10.1	0.91
Current menopausal hormone therapy users												
Adrenal androgens												
DHEA	4.37 (3.73, 5.12)	4.50 (3.88, 5.21)	3.58 (2.89, 4.43)	3.75 (3.24, 4.35)	−14.2	0.02	4.32 (3.68, 5.06)	4.47 (3.85, 5.20)	3.60 (2.91, 4.46)	3.81 (3.28, 4.43)	−11.8	0.05
DHEAS	1022 (850, 1229)	1068 (891, 1280)	940 (769, 1147)	845 (719, 995)	−17.3	0.04	985 (815, 1190)	1054 (877, 1267)	956 (783, 1168)	885 (746, 1049)	−10.2	0.21
Androstenedione	1.32 (1.18, 1.48)	1.25 (1.11, 1.41)	1.16 (1.01, 1.34)	1.17 (1.04, 1.31)	−11.4	0.10	1.31 (1.17, 1.47)	1.25 (1.11, 1.41)	1.16 (1.01, 1.35)	1.17 (1.04, 1.32)	−10.7	0.13
Testosterone	0.51 (0.45, 0.59)	0.50 (0.44, 0.57)	0.47 (0.39, 0.56)	0.51 (0.45, 0.58)	0.0	0.94	0.51 (0.44, 0.58)	0.50 (0.44, 0.57)	0.47 (0.40, 0.56)	0.52 (0.46, 0.59)	2.0	0.76
Ratios												

	Model 1[a]						Model 1 + BMI[b]					
	Recreational physical activity (MET-hour/week)						Recreational physical activity (MET-hour/week)					
	0	0.1–7.4	7.5–14.9	≥15.0	%Δ[c]	p-trend[d]	0	0.1–7.4	7.5–14.9	≥15.0	%Δ[c]	p-trend[d]
DHEAS: DHEA	234 (205, 267)	238 (211, 268)	263 (226, 305)	225 (202, 251)	−3.8	0.71	228 (199, 261)	235 (209, 265)	266 (229, 308)	232 (208, 259)	1.8	0.71
Unconjugated estrone: Androstenedione	161 (129, 201)	195 (161, 236)	234 (173, 316)	205 (167, 251)	27.3	0.11	165 (131, 206)	197 (162, 239)	231 (171, 312)	199 (161, 246)	20.6	0.23
Unconjugated estradiol: Testosterone	86.5 (69.0, 108)	102 (81.0, 128)	114 (85.5, 153)	83.5 (66.1, 105)	−3.5	0.64	85.3 (67.6, 108)	101 (80.4, 128)	115 (85.8, 155)	84.9 (67.0, 107)	−0.5	0.81

[a] Model 1 includes age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), blood draw year (1993–1996, 1997–1998), race (White, Black/Asian/American Indian/Other), smoking status (never, former, current), time since menopause (<10 years, 10–19 years, ≥20 years, missing), alcohol drinking (yes, no, missing), parous (yes, no), family history of breast or ovarian cancer (yes, no), and, among menopausal hormone therapy users, menopausal hormone therapy use (never, former)

[b] Model 1 plus additionally adjustment for BMI (kg/m^2, continuous)

[c] %Δ indicates the percentage change in androgen/androgen metabolite levels, comparing women with the highest vs. lowest categories, and was estimated by taking the ratio of the geometric mean difference in androgen/androgen metabolite levels between women with highest vs. lowest categories to the geometric mean of women with lowest category, multiplied by 100

[d] p-trend was estimated using the Wald test for a continuous physical activity variable.

Table 3.

Geometric means (pmol/L) and 95% confidence intervals (CI) of serum androgen metabolites and ratios by recreational physical activity in postmenopausal women, stratified by menopausal hormone therapy use: the Women's Health Initiative Observational Study

	Model 1[a]						Model 1 + adrenal androgens[b]					
	Recreational physical activity (MET-hour/week)						Recreational physical activity (MET-hour/week)					
	0	0.1–7.4	7.5–14.9	≥15.0	%Δ[c]	p-trend[d]	0	0.1–7.4	7.5–14.9	≥15.0	%Δ[c]	p-trend[d]
Never/former menopausal hormone therapy users												
5α-reduced metabolites												
5α-androstanedione	1.34 (1.19, 1.51)	1.29 (1.15, 1.44)	1.30 (1.16, 1.46)	1.30 (1.17, 1.45)	−3.0	0.78	1.34 (1.16, 1.56)	1.29 (1.13, 1.48)	1.30 (1.13, 1.50)	1.30 (1.13, 1.50)	−3.0	0.76
DHT	0.18 (0.16, 0.20)	0.18 (0.16, 0.20)	0.18 (0.17, 0.20)	0.20 (0.18, 0.22)	11.1	0.05	0.18 (0.16, 0.21)	0.18 (0.16, 0.21)	0.18 (0.16, 0.21)	0.20 (0.17, 0.24)	11.1	0.07
DHTS	0.94 (0.81, 1.09)	0.97 (0.84, 1.13)	1.04 (0.90, 1.20)	1.09 (0.95, 1.25)	16.0	0.07	0.93 (0.83, 1.05)	1.03 (0.91, 1.17)	1.05 (0.92, 1.19)	1.07 (0.93, 1.23)	15.1	0.14
ADT	0.55 (0.50, 0.61)	0.52 (0.47, 0.57)	0.56 (0.51, 0.61)	0.57 (0.52, 0.63)	3.6	0.21	0.55 (0.49, 0.61)	0.53 (0.48, 0.58)	0.56 (0.51, 0.62)	0.57 (0.51, 0.63)	3.6	0.31
ADT-G	22.4 (18.8, 26.7)	18.9 (15.3, 23.3)	19.2 (16.3, 22.5)	21.2 (18.2, 24.7)	−5.4	0.91	21.9 (18.1, 26.4)	21.1 (17.5, 25.4)	19.5 (16.5, 23.0)	20.4 (16.9, 24.6)	−6.8	0.37
3α-diol-3G	1.57 (1.30, 1.88)	1.45 (1.17, 1.81)	1.36 (1.13, 1.64)	1.55 (1.31, 1.84)	−1.3	0.99	1.53 (1.27, 1.84)	1.61 (1.33, 1.96)	1.38 (1.15, 1.67)	1.49 (1.24, 1.81)	−2.6	0.43
3α-diol-17G	1.29 (1.11, 1.50)	1.16 (0.98, 1.38)	1.16 (1.00, 1.34)	1.23 (1.07, 1.42)	−4.7	0.82	1.27 (1.07, 1.52)	1.24 (1.05, 1.47)	1.17 (0.99, 1.38)	1.21 (1.01, 1.44)	−4.7	0.48
Marker of tissue-level androgenic activity												
Sum of ADT-G, 3α-diol-3G, 3α-diol-17G	25.9 (22.0, 30.5)	22.0 (18.0, 26.9)	22.1 (18.9, 25.8)	24.5 (21.1, 28.3)	−5.4	0.85	25.3 (21.3, 30.1)	24.5 (20.6, 29.2)	22.4 (19.1, 26.2)	23.5 (19.7, 28.1)	−7.1	0.31
5β-reduced metabolites												
Etio-G	38.6 (32.3, 46.2)	34.2 (27.6, 42.3)	34.9 (29.1, 41.9)	39.4 (33.0, 47.1)	2.1	0.62	37.7 (30.7, 46.2)	38.5 (31.7, 46.9)	35.5 (29.4, 42.9)	37.7 (30.6, 46.6)	0.0	0.83
Ratios												
DHTS: DHT	5.21 (4.36, 6.22)	5.42 (4.54, 6.46)	5.65 (4.83, 6.61)	5.40 (4.60, 6.33)	3.6	0.72	5.16 (4.21, 6.34)	5.66 (4.66, 6.86)	5.68 (4.72, 6.85)	5.32 (4.36, 6.48)	3.1	0.93
Current menopausal hormone therapy users												
5α-reduced metabolites												

	Model 1[a]						Model 1 + adrenal androgens[b]					
	Recreational physical activity (MET-hour/week)						Recreational physical activity (MET-hour/week)					
	0	0.1–7.4	7.5–14.9	≥15.0	%Δ[c]	p-trend[d]	0	0.1–7.4	7.5–14.9	≥15.0	%Δ[c]	p-trend[d]
5α-androstanedione	1.30 (1.14, 1.47)	1.26 (1.13, 1.39)	1.39 (1.21, 1.61)	1.45 (1.29, 1.64)	11.5	0.09	1.30 (1.14, 1.48)	1.26 (1.11, 1.43)	1.39 (1.21, 1.61)	1.45 (1.29, 1.63)	11.5	0.09
DHT	0.21 (0.18, 0.24)	0.22 (0.20, 0.25)	0.20 (0.17, 0.23)	0.20 (0.18, 0.23)	−4.8	0.28	0.20 (0.17, 0.24)	0.21 (0.19, 0.24)	0.19 (0.17, 0.22)	0.20 (0.18, 0.23)	0.0	0.65
DHTS	0.96 (0.79, 1.17)	1.03 (0.87, 1.22)	0.92 (0.77, 1.10)	0.97 (0.82, 1.14)	1.0	0.77	0.90 (0.74, 1.10)	0.95 (0.79, 1.14)	0.90 (0.74, 1.10)	0.98 (0.81, 1.18)	8.9	0.47
ADT	0.48 (0.44, 0.52)	0.54 (0.49, 0.59)	0.47 (0.42, 0.52)	0.51 (0.47, 0.55)	6.3	0.99	0.47 (0.43, 0.52)	0.52 (0.47, 0.58)	0.47 (0.42, 0.53)	0.51 (0.46, 0.55)	8.5	0.53
ADT-G	16.3 (13.0, 20.5)	16.5 (13.5, 20.2)	15.8 (12.3, 20.1)	14.3 (11.7, 17.5)	−12.3	0.30	14.4 (10.9, 19.2)	13.9 (10.7, 18.1)	15.2 (11.7, 19.7)	14.8 (11.5, 19.0)	2.8	0.66
3α-diol-3G	1.32 (1.07, 1.63)	1.37 (1.16, 1.61)	1.13 (0.92, 1.39)	1.13 (0.96, 1.34)	−14.4	0.13	1.19 (0.93, 1.51)	1.18 (0.93, 1.51)	1.10 (0.86, 1.40)	1.16 (0.92, 1.48)	−2.5	0.73
3α-diol-17G	0.84 (0.69, 1.03)	0.91 (0.77, 1.08)	0.76 (0.65, 0.90)	0.70 (0.59, 0.82)	−16.7	0.02	0.78 (0.64, 0.94)	0.81 (0.71, 0.93)	0.74 (0.65, 0.85)	0.71 (0.62, 0.82)	−9.0	0.21
Marker of tissue-level androgenic activity												
Sum of ADT-G, 3α-diol-3G, 3α-diol-17G	18.9 (15.2, 23.5)	19.4 (16.1, 23.3)	17.9 (14.2, 22.6)	16.4 (13.6, 19.9)	−13.2	0.22	16.8 (12.9, 21.9)	16.4 (12.9, 20.9)	17.2 (13.5, 22.0)	16.9 (13.4, 21.5)	0.6	0.82
5β-reduced metabolites												
Etio-G	36.3 (29.3, 45.0)	35.5 (30.0, 42.1)	33.7 (27.5, 41.4)	30.2 (25.4, 36.0)	−16.8	0.16	32.3 (25.1, 41.6)	30.2 (23.2, 39.2)	32.5 (25.4, 41.6)	31.2 (23.9, 40.6)	−3.4	0.95
Ratios												
DHTS: DHT	4.59 (3.72, 5.66)	4.66 (3.96, 5.49)	4.70 (3.89, 5.67)	4.81 (4.04, 5.73)	4.8	0.69	4.45 (3.58, 5.52)	4.46 (3.73, 5.33)	4.65 (3.77, 5.73)	4.85 (4.01, 5.87)	9.0	0.38

[a] Model 1 includes age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), blood draw year (1993–1996, 1997–1998), race (White, Black/Asian/American Indian/Other), smoking status (never, former, current), time since menopause (<10 years, 10–19 years, ≥20 years, missing), alcohol drinking (yes, no, missing), parous (yes, no), family history of breast or ovarian cancer (yes, no), BMI (kg/m^2, continuous), and, among menopausal hormone therapy users, menopausal hormone therapy use (never, former)

[b] Model 1 plus additionally adjustment for summed concentrations of adrenal androgens (pmol/L, continuous)

[c] %Δ indicates the percentage change in androgen/androgen metabolite levels, comparing women with the highest vs. lowest categories, and was estimated by taking the ratio of the geometric mean difference in androgen/androgen metabolite levels between women with highest vs. lowest categories to the geometric mean of women with lowest category, multiplied by 100

[d] p-trend was estimated using the Wald test for a continuous physical activity variable.

Table 4.

Geometric means (pmol/L) and 95% confidence intervals (CI) of serum adrenal androgens and ratios by sitting time in postmenopausal women, stratified by menopausal hormone therapy use: the Women's Health Initiative Observational Study

	Model 1[a]					Model 1 + BMI[b]				
	Sitting time (hour/day)					Sitting time (hour/day)				
	≤5	6–9	≥10	%Δ[c]	p-trend[d]	≤5	6–9	≥10	%Δ[c]	p-trend[d]
Never/former menopausal hormone therapy users										
Adrenal androgens										
DHEA	4.89 (4.34, 5.52)	4.79 (4.21, 5.45)	5.04 (4.33, 5.86)	3.1	0.79	4.95 (4.38, 5.61)	4.82 (4.23, 5.49)	5.08 (4.36, 5.90)	2.6	0.84
DHEAS	1064 (917, 1235)	1089 (941, 1261)	1088 (925, 1279)	2.3	0.81	1102 (945, 1286)	1108 (955, 1285)	1112 (945, 1307)	0.9	0.93
Androstenedione	1.38 (1.26, 1.51)	1.41 (1.28, 1.55)	1.53 (1.38, 1.70)	10.9	0.11	1.39 (1.27, 1.53)	1.42 (1.29, 1.56)	1.54 (1.38, 1.71)	10.8	0.12
Testosterone	0.56 (0.50, 0.63)	0.55 (0.49, 0.61)	0.61 (0.52, 0.73)	8.9	0.32	0.56 (0.50, 0.63)	0.55 (0.49, 0.61)	0.62 (0.52, 0.73)	10.7	0.34
Ratios										
DHEAS: DHEA	217 (194, 244)	227 (206, 251)	216 (196, 238)	−0.5	0.96	222 (198, 250)	230 (208, 253)	219 (199, 241)	−1.4	0.91
Unconjugated estrone: Androstenedione	38.3 (34.3, 42.6)	41.3 (36.3, 46.9)	44.2 (37.1, 52.6)	15.4	0.10	41.0 (37.0, 45.6)	42.6 (37.8, 48.1)	46.1 (38.9, 54.8)	12.4	0.19
Unconjugated estradiol: Testosterone	20.2 (16.8, 24.1)	25.4 (21.0, 30.9)	23.4 (18.0, 30.4)	15.8	0.17	23.6 (20.0, 27.8)	27.4 (23.3, 32.1)	25.8 (20.2, 32.8)	9.3	0.37
Current menopausal hormone therapy users										
Adrenal androgens										
DHEA	4.59 (3.96, 5.31)	3.63 (3.15, 4.18)	4.13 (3.55, 4.81)	−10.0	0.19	4.63 (3.99, 5.38)	3.64 (3.15, 4.20)	4.08 (3.50, 4.75)	−11.9	0.12
DHEAS	1059 (922, 1215)	825 (705, 965)	1065 (900, 1259)	0.6	0.83	1080 (937, 1246)	832 (709, 975)	1036 (875, 1227)	−4.1	0.48
Androstenedione	1.35 (1.22, 1.51)	1.09 (0.99, 1.20)	1.27 (1.14, 1.42)	−5.9	0.25	1.36 (1.22, 1.51)	1.10 (1.00, 1.21)	1.26 (1.13, 1.41)	−7.4	0.19
Testosterone	0.53 (0.47, 0.60)	0.48 (0.43, 0.54)	0.50 (0.44, 0.57)	−5.7	0.41	0.53 (0.47, 0.60)	0.49 (0.43, 0.54)	0.49 (0.43, 0.56)	−7.5	0.31
Ratios										
DHEAS: DHEA	231 (206, 259)	228 (203, 254)	258 (232, 286)	11.7	0.14	233 (208, 261)	228 (204, 255)	254 (229, 282)	9.0	0.25
Unconjugated estrone: Androstenedione	147 (121, 179)	248 (205, 300)	197 (161, 242)	34.0	0.01	144 (118, 177)	246 (203, 298)	202 (163, 249)	40.3	0.004
Unconjugated estradiol: Testosterone	75.5 (60.7, 94.0)	106 (86.4, 130)	105 (81.0, 135)	39.1	0.02	75.9 (61.0, 94.4)	106 (86.5, 130)	104 (80.0, 135)	37.0	0.03

[a] Model 1 includes age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), blood draw year (1993–1996, 1997–1998), race (White, Black/Asian/American Indian/Other), smoking status (never, former, current), time since menopause (<10 years, 10–19 years, ≥20 years, missing), alcohol drinking (yes, no, missing), parous (yes, no), family history of breast or ovarian cancer (yes, no), and, among menopausal hormone therapy users, menopausal hormone therapy use (never, former)

[b] Model 1 plus additionally adjustment for BMI (kg/m^2, continuous)

[c] %Δ indicates the percentage change in androgen/androgen metabolite levels, comparing women with the highest vs. lowest categories, and was estimated by taking the ratio of the geometric mean difference in androgen/androgen metabolite levels between women with highest vs. lowest categories to the geometric mean of women with lowest category, multiplied by 100

[d] p-trend was estimated using the Wald test for a continuous sitting time variable.

Table 5.

Geometric means (pmol/L) and 95% confidence intervals (CI) of serum androgen metabolites and ratios by sitting time in postmenopausal women, stratified by menopausal hormone therapy use: the Women's Health Initiative Observational Study

	Model 1[a]					Model 1 + adrenal androgens[b]				
	Sitting time (hour/day)					Sitting time (hour/day)				
	≤5	6–9	≥10	%Δ[c]	p-trend[d]	≤5	6–9	≥10	%Δ[c]	p-trend[d]
Never/former menopausal hormone therapy users										
5α-reduced metabolites										
5α-androstanedione	1.36 (1.23, 1.50)	1.30 (1.19, 1.43)	1.27 (1.13, 1.42)	−6.6	0.24	1.36 (1.20, 1.54)	1.30 (1.14, 1.49)	1.27 (1.10, 1.45)	−6.6	0.23
DHT	0.18 (0.17, 0.20)	0.18 (0.17, 0.20)	0.20 (0.18, 0.22)	11.1	0.30	0.18 (0.16, 0.21)	0.18 (0.16, 0.21)	0.20 (0.16, 0.24)	11.1	0.34
DHTS	0.96 (0.85, 1.10)	1.00 (0.88, 1.13)	1.10 (0.95, 1.28)	14.6	0.12	0.98 (0.88, 1.09)	1.00 (0.90, 1.11)	1.10 (0.95, 1.26)	12.2	0.15
ADT	0.54 (0.50, 0.58)	0.56 (0.52, 0.61)	0.55 (0.50, 0.61)	1.9	0.58	0.54 (0.50, 0.59)	0.56 (0.51, 0.62)	0.55 (0.49, 0.61)	1.9	0.69
ADT-G	20.2 (17.3, 23.6)	19.2 (16.6, 22.3)	22.5 (18.9, 26.8)	11.4	0.42	20.7 (17.5, 24.5)	19.4 (16.7, 22.7)	22.2 (18.5, 26.6)	7.2	0.56
3α-diol-3G	1.36 (1.15, 1.60)	1.52 (1.30, 1.78)	1.59 (1.28, 1.96)	16.9	0.12	1.39 (1.17, 1.65)	1.54 (1.31, 1.80)	1.57 (1.28, 1.91)	12.9	0.14
3α-diol-17G	1.22 (1.07, 1.39)	1.19 (1.05, 1.36)	1.23 (1.05, 1.45)	0.8	0.96	1.24 (1.06, 1.44)	1.20 (1.04, 1.39)	1.22 (1.01, 1.48)	−1.6	0.84
Marker of tissue-level androgenic activity										
Sum of ADT-G, 3α-diol-3G, 3α-diol-17G	23.2 (20.0, 26.9)	22.4 (19.5, 25.8)	26.0 (21.9, 30.7)	12.1	0.35	23.7 (20.2, 27.8)	22.7 (19.6, 26.2)	25.6 (21.6, 30.4)	8.0	0.46
5β-reduced metabolites										
Etio-G	34.3 (29.1, 40.4)	38.4 (32.8, 45.0)	38.2 (31.0, 46.9)	11.4	0.29	35.2 (29.3, 42.2)	38.9 (32.9, 46.0)	37.6 (30.7, 46.1)	6.8	0.35
Ratios										
DHTS: DHT	5.25 (4.52, 6.11)	5.44 (4.72, 6.27)	5.58 (4.71, 6.62)	6.3	0.53	5.30 (4.44, 6.33)	5.47 (4.61, 6.47)	5.55 (4.48, 6.89)	4.7	0.61
Current menopausal hormone therapy users										
5α-reduced metabolites										
5α-androstanedione	1.39 (1.26, 1.54)	1.41 (1.27, 1.56)	1.20 (1.07, 1.34)	−13.7	0.05	1.39 (1.27, 1.53)	1.41 (1.27, 1.56)	1.20 (1.05, 1.37)	−13.7	0.05
DHT	0.21 (0.19, 0.24)	0.21 (0.19, 0.23)	0.20 (0.18, 0.23)	−4.8	0.57	0.21 (0.18, 0.23)	0.21 (0.19, 0.23)	0.20 (0.17, 0.22)	−4.8	0.52
DHTS	1.01 (0.87, 1.17)	0.96 (0.83, 1.11)	0.96 (0.80, 1.15)	−5.0	0.59	0.95 (0.80, 1.12)	0.96 (0.81, 1.14)	0.89 (0.74, 1.08)	−6.3	0.51
ADT	0.50 (0.46, 0.53)	0.50 (0.46, 0.54)	0.51 (0.47, 0.55)	2.0	0.59	0.49 (0.44, 0.54)	0.50 (0.46, 0.55)	0.50 (0.45, 0.55)	2.0	0.60
ADT-G	17.7 (14.7, 21.3)	14.3 (11.9, 17.1)	15.2 (12.6, 18.4)	−14.1	0.16	15.7 (12.2, 20.1)	14.4 (11.4, 18.3)	13.2 (10.2, 16.9)	−15.9	0.07
3α-diol-3G	1.33 (1.13, 1.57)	1.17 (1.01, 1.35)	1.24 (1.06, 1.45)	−6.8	0.47	1.20 (0.95, 1.51)	1.18 (0.95, 1.46)	1.10 (0.87, 1.38)	−8.3	0.34
3α-diol-17G	0.83 (0.71, 0.97)	0.78 (0.67, 0.91)	0.80 (0.68, 0.95)	−3.6	0.75	0.76 (0.67, 0.87)	0.79 (0.69, 0.90)	0.72 (0.62, 0.85)	−5.3	0.64

	Model 1[a]					Model 1 + adrenal androgens[b]				
	Sitting time (hour/day)					Sitting time (hour/day)				
	≤5	6–9	≥10	%Δ[c]	p-trend[d]	≤5	6–9	≥10	%Δ[c]	p-trend[d]
Marker of tissue-level androgenic activity										
Sum of ADT-G, 3α-diol-3G, 3α-diol-17G	20.2 (16.9, 24.2)	16.6 (14.0, 19.6)	17.6 (14.7, 21.1)	−12.9	0.18	18.0 (14.2, 22.8)	16.8 (13.5, 20.9)	15.3 (12.1, 19.4)	−15.0	0.08
5β-reduced metabolites										
Etio-G	38.2 (32.7, 44.8)	29.4 (25.3, 34.2)	34.8 (29.7, 40.9)	−8.9	0.28	34.2 (26.9, 43.4)	29.7 (23.4, 37.6)	30.4 (23.8, 38.7)	−11.1	0.13
Ratios										
DHTS: DHT	4.75 (4.04, 5.58)	4.64 (3.94, 5.46)	4.71 (3.95, 5.61)	−0.8	0.92	4.60 (3.84, 5.52)	4.65 (3.90, 5.54)	4.53 (3.76, 5.47)	−1.5	0.90

[a] Model 1 includes age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), blood draw year (1993–1996, 1997–1998), race (White, Black/Asian/American Indian/Other), smoking status (never, former, current), time since menopause (<10 years, 10–19 years, ≥20 years, missing), alcohol drinking (yes, no, missing), parous (yes, no), family history of breast or ovarian cancer (yes, no), BMI (kg/m^2, continuous), and, among menopausal hormone therapy users, menopausal hormone therapy use (never, former)

[b] Model 1 plus additionally adjustment for summed concentrations of adrenal androgens (pmol/L, continuous)

[c] %Δ indicates the percentage change in androgen/androgen metabolite levels, comparing women with the highest vs. lowest categories, and was estimated by taking the ratio of the geometric mean difference in androgen/androgen metabolite levels between women with highest vs. lowest categories to the geometric mean of women with lowest category, multiplied by 100

[d] p-trend was estimated using the Wald test for a continuous sitting time variable.