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Symptoms in peri- and postmenopausal women in relation to testosterone concentrations. Data from;

The Women's Health in the Lund Area

(WHILA) study.

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**Short title:** Women and testosterone

**Key-words;** climacteric, perimenopause, Testosterone, Androgens, Quality of Life

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## **Abstract**

*Objectives:* The aim of this study was to investigate possible associations between androgen concentrations in perimenopausal women and symptoms that may be associated with low androgen concentrations in the blood.

*Methods:* All women born 1935 to 1945 living in a defined geographic area in Sweden (n=10766) were invited to a screening program that included physical and laboratory examinations and a questionnaire. Three groups were identified; premenopausal women, women on hormone replacement therapy (HRT) and postmenopausal women without HRT. Concentrations of testosterone (T), androstendione, Sex Hormone Binding Globulin and estradiol were measured. Waist Hip Ratio, Body Mass Index and Free Testosterone Index (FTI) were calculated.

*Results:* 6908 women participated. The women on HRT had lower T and FTI and were less satisfied with mood and energy ( $p<0.05$ ). Women with hot flushes had higher T and FTI and women reporting coldness had lower concentrations ( $p<0.05$ ). Sexual well-being were not correlated to T or FTI ( $p>0.05$ ).

*Conclusions:* Lower T concentrations were associated with lower quality of life in perimenopausal women but not to sexual well-being. There must be other factors than

decrements in sex hormones that contribute to the emergence of some perimenopausal symptoms.

## **Introduction**

The symptoms associated with falling estrogen concentrations during the menopausal transition are quite well known. Hot flushes are the most common symptom, probably caused by effects of sex steroids on the thermoregulatory centre in hypothalamus<sup>1,2</sup>. In the past few years the interest in the role of androgens during the menopausal transition has increased significantly. Androgen insufficiency in women has been suggested to be manifested in a diminished sense of well-being or dysphoric mood, depressed mood, persistent unexplained fatigue and changed sexual function. These changes have been observed in association with low or falling androgen concentrations due to e.g. oophorectomy, hypopituitarism, adrenal insufficiency or ovarian failure<sup>3</sup>.

Female sexual dysfunction may at least partly be a result of low androgen levels<sup>4-6</sup>, although one study has shown no such correlation<sup>7</sup>. Therapy with estrogen combined with testosterone (T) has shown to increase sexual well-being and libido more than estrogens given alone in single blind studies<sup>8,9</sup> as well as in double blind studies<sup>10,11</sup>. Less specific symptoms related to menopause, such as changes in memory, sleep, cognition, decreasing bone mass and muscle strength have been associated with low T concentrations<sup>3,12</sup>. However, the role of T in memory functioning seems to depend on which kind of memory is analysed<sup>13-15</sup>.

The association between T concentrations and fat distribution or waist hip ratio (WHR) has been investigated but the results are diverse. T may have different effects depending on if it is the so called female (subcutaneous fat) or the male (visceral fat) obesity that is considered<sup>16-19</sup>. Steroid Hormone Binding Globulin (SHBG) concentrations are in some studies negatively correlated with body mass index (BMI) and WHR<sup>17,20-23</sup>.

Most of the circulating T is firmly bound to SHBG, synthesized in the liver. A significant amount of T is also loosely bound to albumin, leaving only a small fraction of free circulating T. The effects of estradiol on SHBG levels have been studied during the climacteric period, where higher estrogen levels have been associated with higher SHBG levels<sup>23</sup>. Investigations on when and how much total T, free T and SHBG change due to the menopausal transition have shown different results<sup>23-31</sup>. Androstendione (A), which is derived from the adrenal gland and the ovaries, needs to be converted to T to have potent androgenic effects<sup>32</sup>. In men, plasma T concentrations decline with age<sup>33</sup>. Bioavailable T, i.e. free T and T bound to albumin, seems positively associated with libido in men and subsequent T treatment in elderly men result in improvement<sup>34,35</sup>. T treatment also increases muscle mass and muscle strength<sup>36,37</sup> in older men and is proposed to ameliorate some other conditions related to T deficiency, e.g. osteoporosis in older men<sup>38</sup>.

It is possible that these T deficiency symptoms are similar in women and men or that they may be manifested more vaguely in women. Studies on symptoms possibly related to T deficiency have been performed on smaller numbers of women (12-226 women)<sup>4-7,11,39,40</sup> than on men. Therefore this study aims at delineating perceived associations between serum androgens and symptoms as well as signs attributed to low androgen influence in a large population based cohort of perimenopausal women.

## Methods

### *Subjects*

All women (n=10766) who were born between 2 December 1935 and 1 December 1945 and living in the Lund area in Sweden by 1 December 1995 were invited to a screening program that was performed from 2 December 1995 until 3 February 2000. The program included a questionnaire, physical examination and hormone measurements. The women were identified through a population register comprising all inhabitants. Informed consent was obtained from all participants and the study was approved by the ethics committee at Lund University<sup>41</sup>.

The population was divided into three groups based on their menopausal status: PM; premenopausal women, i.e. women with preserved cyclic menstrual bleeding, PMT; women on hormone replacement therapy (HRT), and PMO; postmenopausal women without HRT. Definition of menopause was a bleeding-free interval of at least 12 months. The study design has been presented elsewhere in more detail<sup>41-43</sup>.

### *Physical Examination*

Body weight, height, minimal waist and maximal hip circumference were measured. BMI was calculated as kg/m<sup>2</sup>. WHR was calculated as the circumference of the waist divided by the circumference of the hip.

### *Laboratory Analyses*

T and estradiol were measured with KRYPTOR®, an immunofluorescent assay using KRYPTOR®-Testosterone and KRYPTOR®-Estradiol 17β kits (B.R.A.H.M.S Ag., Germany). Kryptor® is based on TRACE® (Time Resolved Amplified Cryptate Emission)

technology, which is a non-radioactive technology. Commercial ELISA methods with monoclonal antibodies (DRG Instrument GmbH, Germany) were used when measuring SHBG and androstendione. Coefficients of variance for the hormones were: T 6.4%, estradiol 6.0%, androstendione 6.0% and for SHBG 3.0%. Lower detection limit for estradiol was 3.5 pmol/L. Estradiol levels below 3.5 pmol/L were set as 2.625 pmol/L. This level was a theoretical calculated median of the values below 3.5 pmol/L, based on the normal distribution.

A Free T Index (FTI), calculated as  $T/SHBG \times 100$ , was used as a measurement of estimated free T.

### *Symptoms*

From the questionnaire items regarding Quality of Life (QoL); i.e. memory, physical fitness, mood, energy, patience, self-confidence, sleep and sexual well-being were analysed. On every question the women were to mark on a seven step Likert scale from one to seven (1 being “very bad“, and 7 being “terrific, couldn’t be better“).

Questions on hot flushes and vaginal dryness were answered “yes” or “no”, depending on if the women reported the symptoms at the moment or not. In the questionnaire, there were also questions that investigated whether the women had or had not (yes or no) experienced a specific symptom during the past three months.

### *Statistics*

SPSS version and 12.01 (SPSS Inc, Chicago, Il, USA) was used for all statistical calculations. One-way ANOVA was used for comparisons of means between the three groups (PM, PMT, PMO) regarding BMI, WHR and some of the QoL questions. The Bonferroni method was

used to adjust for multiple comparisons when differences between individual groups were considered.

Since the hormone and SHBG levels did not show normal distribution Kruskal-Wallis H and Mann-Whitney U tests were used to analyze differences between the groups.

$\chi^2$ -test was used to analyze differences in categorized data between groups according to menopausal status.

Mann-Whitney U test was performed regarding T levels and FTI between the women who answered yes or no on the questions concerning symptoms. On the questions where significant differences were found, we also analysed differences within the groups according to menopausal status.

We analysed correlations between grades on the seven step-score of the different QoL questions and T levels as well as FTI. The natural logarithm of SHBG (ln SHBG) was used when correlations with BMI and WHR were analysed since ln SHBG was more nearly normally distributed.

To analyse the QoL questions as categorized variables the different scores (1-7) were grouped into three new groups. Group 1 consisted of those who marked score one or two, group 2 those marking three, four or five, and group 3 those who marked score six or seven. Group 1 was considered to consist of those having bad QoL, group 2 those having fair QoL and group 3 those having good or very good QoL. The means were then compared with one-way ANOVA and with post-hoc Bonferroni.

Multiple linear regression analysis was used to investigate which factors may have an impact on the SHBG levels and how these factors may be connected with SHBG. The independent factors that were analysed with ln SHBG as dependent variable were testosterone, estradiol, age, WHR and BMI.

A p-value<0.05 was considered significant.

## Results

6908 of totally 10766 invited women (64.2%) were included in the study, i.e. answered the questionnaire and underwent the examinations and hormone measurements. Since all women did not answer all questions in the questionnaire and did not take part in all physical and laboratory examinations, complete results were not obtained from every woman. For each parameter the exact number (n) of included women is noted in the tables. The overall mean age for all women (n=6908) was 56.4 years ( $\pm 3.0$ ).

Analyses regarding education, degree of working, and the pattern of physical activity have been reported in earlier WHILA studies [42].

**Table 1** Descriptive data according to perimenopausal status on current report of hot flushes, vaginal dryness, hormone concentrations, BMI and WHR.

|                          | <b>PM</b><br>n=492               | <b>PMT</b><br>n=2816              | <b>PMO</b><br>n=3600                  |
|--------------------------|----------------------------------|-----------------------------------|---------------------------------------|
| Age (years)              | 53.3*<br>( $\pm 1.6$ ; n=492)    | 56.3***<br>( $\pm 2.9$ ; n=2816)  | 57.0<br>( $\pm 3.0$ ; n=3600)         |
| Hot Flushes %            | 31.1* (n=143)                    | 59.0** (n=1490)                   | 55.1 (n=1780)                         |
| Vaginal dryness %        | 17.1* (n=80)                     | 29.2** (n=731)                    | 37.4 (n=1199)                         |
| T (nmol/L)               | 2.08<br>(1.19-3.00; n=462)       | 1.81***<br>(0.89-2.75; n=2657)    | 2.10<br>(1.19-3.04; n=3333)           |
| SHBG (nmol/L)            | 57.1**<br>(38.9-80.2; n=463)     | 64.6***<br>(44.7-91.3; n=2657)    | 51.8<br>(35.2-73.6; n=3341)           |
| FTI                      | 3.55<br>(1.83-5.93; n=460)       | 2.54***<br>(1.17-4.81; n=2646)    | 3.77<br>(1.93-6.65; n=3322)           |
| Estradiol (pmol/L)       | 95.6**<br>(28-233; n=463)        | 85.4***<br>(34-161; n=2653)       | 15.3<br>(5.2-34.0; n=3331)            |
| A (nmol/L)               | 4.17<br>(3.07-5.80; n=462)       | 3.69***<br>(2.59-5.24; n=2658)    | 4.11<br>(2.76-5.87; n=3328)           |
| BMI (kg/m <sup>2</sup> ) | 25.1<br>( $\pm 4.36$ ; n=492)    | 25.0<br>( $\pm 3.79$ ; n=2816)    | 25.9****<br>( $\pm 4.39$ ; n=3600)    |
| WHR                      | 0.771<br>( $\pm 0.0611$ ; n=490) | 0.775<br>( $\pm 0.0625$ ; n=2809) | 0.786****<br>( $\pm 0.0685$ ; n=3588) |

T, SHBG, FTI, Estradiol and A are expressed in median and inter quartile range (IQR). Age, BMI and WHR are expressed as mean and standard deviations. The number of people is noted (n) for each analysis.

\* p<0.05 compared to PMT and PMO

\*\* p<0.05 compared to PMO

\*\*\* p<0.05 compared to PM and PMO

\*\*\*\* p<0.001 compared to PM and PMT

Detailed prevalences of hot flushes and vaginal dryness in the studied women have been reported before [42]. At the moment, PMT women experienced a higher degree of hot flushes than the PM and PMO women respectively and PMO women reported vaginal dryness more often than the other groups ( $p < 0.05$ , Table 1).

### *Hormone measurements and BMI and WHR*

Total T levels were lower in the PMT women ( $p < 0.05$ ) than in the other groups. PMT women had higher levels of SHBG than the others and the PMO women had lower SHBG levels than the PM women ( $p < 0.05$ ). FTI was lower in the PMT group compared to the others. Estradiol levels were highest in the premenopausal women, whereas the PMT women had higher levels than the PMO women ( $p < 0.05$ ). The PMT women also had lower levels of A than the others ( $p < 0.05$ , Table 1). In the PMT group women with oral HRT had lower FTI ( $n = 1375$ , median 2.31 IQR 1.12-4.21) and A ( $n = 1380$ , median 3.62 nmol/L; IQR 2.60-5.12) than women with transdermal HRT (FTI 3.21; 1.43-5.67,  $n = 339$  and A 3.95 nmol/L ; 2.73-5.66,  $n = 341$ ;  $p < 0.05$ ). No difference in T was found. We did not do any further analyses since only 61.2 % of the PMT women had specified the HRT used.

7.0 % of the women were oophorectomized but T and FTI were not found to be different when these women were excluded from the analyses.

BMI and WHR were higher in postmenopausal women without HRT ( $p < 0.001$ ) than in the other groups (Table 1).

### *Quality of life questions*

Sexual well-being, sleep and health were significantly better ( $p < 0.05$ ) in the PM group than in the PMT group and the PMO group, but sexual well-being was better in the PMT group than in the PMO group ( $p < 0.05$ ; Table 2).

The PMT group reported lower scores on mood, energy and memory than the PM and PMO group. The difference between the PM and the PMT concerning memory was not, however, significant (Table 2).

No differences in sexual well-being were found in the PMT group between oral and transdermal users of HRT.

**Table 2** Scores on QoL questions according to perimenopausal status (scores 1-7, 1 being “very bad” and 7 being “terrific”).

|                   | PM            | PMT              | PMO           |
|-------------------|---------------|------------------|---------------|
| Sexual well-being | 5.38* (n=458) | 4.93** (n=2642)  | 4.77 (n=3210) |
| Mood              | 5.49 (n=487)  | 5.33*** (n=2796) | 5.42 (n=3558) |
| Energy            | 5.27 (n=489)  | 5.08*** (n=2795) | 5.22 (n=3557) |
| Sleep             | 5.40* (n=489) | 5.12 (n=2805)    | 5.14 (n=3568) |
| Memory            | 5.35 (n=486)  | 5.23** (n=2790)  | 5.32 (n=3559) |
| Health            | 5.62* (n=487) | 5.30 (n=2781)    | 5.31 (n=3535) |
| Physical fitness  | 4.68 (n=488)  | 4.62 (n=2801)    | 4.61 (n=3569) |

\* p<0.05 compared to PMT and PMO

\*\* p<0.05 compared to PMO

\*\*\*p<0.05 compared to PM and PMO

Scores expressed as means

### *Symptoms related to total T concentrations and FTI in all perimenopausal groups*

Women reporting coldness (n=1568) had significantly lower levels of total T (median 1.90 nmol/L) than those who did not report coldness (n=4763, 2.00 nmol/L, p<0.05). Women with

current hot flushes (n=3203) had higher levels of total T (2.02 nmol/L) than women without hot flushes (1.92 nmol/L, n=2608, p<0.05).

The symptoms, which significantly differed with regard to the FTI between the women with and those without symptoms, are shown in Table 3. Women who experienced these symptoms had higher FTI compared to women without symptoms, except coldness where women experiencing coldness had lower FTI.

**Table 3** FTI in women who reported and not reported symptoms including all perimenopausal groups. Only symptoms that showed a significant difference is shown.

|                            | <b>Yes</b>                | <b>No</b>                 | <b>p</b> |
|----------------------------|---------------------------|---------------------------|----------|
| <b>Dizziness</b>           | 3.39 (1.69-6.09) (n=1647) | 3.13 (1.53-5.64) (n=4627) | <0.05    |
| <b>Impaired hearing</b>    | 3.33 (1.67-6.20) (n=1431) | 3.17 (1.53-5.69) (n=4816) | <0.05    |
| <b>Sweats</b>              | 3.51 (1.72-6.63) (n=1966) | 3.07 (1.51-5.43) (n=4317) | <0.05    |
| <b>Coldness</b>            | 2.90 (1.36-5.23) (n=1561) | 3.30 (1.61-5.91) (n=4747) | <0.05    |
| <b>Joint problems</b>      | 3.40 (1.67-6.08) (n=2866) | 3.07 (1.50-5.54) (n=3425) | <0.05    |
| <b>Current Hot flushes</b> | 3.28 (1.61-5.98) (n=3190) | 3.06 (1.49-5.57) (n=2601) | <0.05    |

FTI in median and IQR.

Just as in the whole group, women with sweats, coldness and joint problems had significantly different FTI within the three groups according to menopausal status except for sweats and joint problems within the PM group. Within the PMO and the PMT group, women reporting sweats had higher FTI (median 4.10 and 2.67 respectively) compared to the non-symptomatic women (3.64 and 2.49 respectively, p<0.05). Regarding coldness in the PMO, PMT and the PM group the symptom group had lower FTI (3.47, 2.36 and 3.18 respectively) than the non-symptomatic women (3.86, 2.60 and 3.99 respectively, p<0.05). Within the PMO and the

PMT group the women with joint problems had higher FTI (3.96 and 2.79 respectively) than the women without those problems (3.67 and 2.39 respectively,  $p<0.05$ ).

*Hormone concentrations in women with and without hot flushes at the moment*

The PMT women were not included in these analyses since we wanted to exclude the effect of HRT on the women’s hormone concentrations and ratios. In the summarized PM and PMO groups, women with hot flushes at the moment higher total T concentrations and FTI ratios than the women without hot flushes ( $p<0.05$ ). PMO women who reported hot flushes had higher FTI ( $p<0.05$ ) and total T ( $p<0.05$ ) (Table 4).

**Table 4** Hormone concentrations and ratios in women with and without hot flushes at the moment (including PM and PMO women)

|                          | <b>T</b> (nmol/L) | <b>FTI</b>        |
|--------------------------|-------------------|-------------------|
| <b>Yes</b> (n=1780-1787) | 2.14* (1.20-3.10) | 3.85* (1.99-6.73) |
| <b>No</b> (n=1628-1634)  | 2.00 (1.17-2.92)  | 3.64 (1.76-6.25)  |

\* $p<0.05$  compared to women that did not report hot flushes

Concentrations and ratios are expressed in median and IQR. The n differs since not all analyses were obtained from every woman.

*Correlations*

The QoL questions memory, energy, patience and self-confidence were significant, albeit very weak, correlated with total T concentrations ( $r=0.025-0.036$ ). FTI was very weak correlated with memory ( $r=0.031$ ) and physical fitness ( $r=-0.044$ ). A significant, but weak, positive correlation was found between FTI and WHR ( $r=0.165$ ). No correlation was found between total T and WHR.

A significant negative correlation between ln SHBG and BMI was found ( $r=-0.346$ ) and between ln SHBG and WHR ( $r=-0.329$ ), indicating that higher SHBG is associated with lower WHR and BMI.

### *Grouping into categorical variables*

The women with “bad memory” scores had significantly lower total T concentrations ( $n=118$ ; median 1.67 nmol/L, inter quartile range (IQR) 0.69-2.71) than the women with “neither bad nor very good memory” scores ( $n=3277$ ; 1.94 nmol/L, 1.05-2.86) and the women with “good or very good memory” scores ( $n=2992$ ; 2.04 nmol/L, 1.06-2.98).

The woman with “neither bad nor very good memory” scores had lower FTI ( $n=3260$ ; 3.14, 1.53-5.66) compared to the women with “good or very good memory” scores ( $n=2986$ ; 3.30, 1.61-5.91). The women with bad memory scores had lower FTI ( $n=117$ ; 2.87, 1.21-5.11) than the women with good or very good memory with borderline significance ( $p=0.054$ )

### *Linear regression analysis of ln SHBG*

When running linear regression analysis of ln SHBG with estradiol, T, WHR, BMI and age as explaining factors, the  $R^2$  was 0.199. Estradiol and age seem to increase the SHBG concentrations whereas higher T, WHR and BMI were associated with lower SHBG concentrations. A stepwise regression analysis left BMI, estradiol and WHR as explaining factors for the SHBG concentrations more than T and age. When excluding the PMT women from the analysis the effect of T was not significant and T was therefore excluded from the model. The effect of BMI, WHR, estradiol and age together could explain 20.6 % of ln SHBG ( $R^2=0.206$ ). These variables were used in a stepwise regression analysis where WHR explained most of the variation of ln SHBG. This is somewhat contradictory to the result from the analysis on all women where estradiol was the dominating factor.

## Discussion

In the current study, women with hormone replacement therapy had lower FTI, total T and androstendione concentrations in plasma. We also found that women reporting hot flushes (in all three groups) had higher FTI and total T concentrations. The women reporting coldness had lower total T concentrations and FTI and the women reporting poor memory had lower concentrations of total T. Analyses of SHBG showed that it was negatively correlated with BMI and WHR. No correlations between sexual well-being and FTI or total T were found. The lower A concentrations in the PMT group can possibly be explained by a decreased gonadotrophin drive. It may be speculated that lower adrenal A and T result in androgen deficiency symptoms that have made these women seek medical care and received HRT. Total T concentrations were lower in women using HRT compared to other groups of women in this study, which is in line with another study showing lower T-concentrations when using oral estrogens<sup>44</sup>. These findings were explained as a possible consequence of a decreased gonadotrophin drive to the postmenopausal ovarian stroma. However, one study did not support this finding<sup>39</sup>.

We did not find any difference in total T concentrations between the premenopausal and postmenopausal women, which is in accordance with previous studies<sup>23,27</sup>. However, two smaller studies, one prospective and one cross-sectional, found a fall or a difference in total T over the menopausal transition<sup>26,30</sup>.

Coldness was connected with lower total T and FTI in this study. To speculate, this may be due to androgen effects on the hypothalamic thermoregulatory centre<sup>45</sup>, since receptors for both androgens and estrogens have been found in many different areas of the brain, e.g. in the hypothalamus<sup>46,47</sup>.

Other studies have found positive correlations between total T and BMI<sup>48,49</sup>, and between total T and WHR<sup>49</sup>. This was, however, not the case in our study and could possibly be due to

differences between the women studied in the different studies. In one of the studies there were postmenopausal women<sup>48</sup> and in another pre- and perimenopausal<sup>49</sup>.

It could be argued that we used FTI as an estimated value for free T, but since albumin measurements were not done we were unable to calculate bioavailable T. We found that the estimated free T (FTI) was lower in the PMT group than in the other groups. This is probably due to the lower T and also the higher levels of SHBG when using oral estrogens<sup>44</sup>. Lower free T has been found before in HRT users<sup>39,50</sup>. Between the PM women and the PMO women the estimated free T did not differ significantly even though the SHBG levels were significantly lower in the PMO group. Unchanged free T was seen in other studies<sup>26,28</sup>, but another prospective study has actually shown an increase in free T over the climacteric period<sup>23</sup>.

We found a weak positive correlation between WHR and FTI and this supports an earlier study by Guthrie et al.<sup>18</sup>. Even though total T did not correlate to WHR our study supports the thought that central adiposity, in our study estimated as WHR, is positively correlated with FTI. Women in the PMO group had higher BMI and WHR and it seems like the falling or low estrogen concentrations, as seen in the PMO group, affect BMI and WHR. In another study WHR also increased during the menopausal transition but women with HRT showed no increase in WHR<sup>51</sup>.

The women who reported hot flushes had higher levels of total T and higher FTI, but lower estradiol levels. When excluding the PMT-group from the analysis, the differences in total T and FTI, were still present within the PM- and PMO-groups. It may be that the women experiencing hot flushes have lower estradiol levels, which decrease the negative feedback on the pituitary, which in turn permits higher LH, stimulating androgen production from the ovarian stroma<sup>50,52</sup>.

When running correlation analyses, including all women, of FTI, total T and the QoL scores, very weak correlations were found. Of these scores, memory and energy were significantly correlated with total T and memory correlated, though weakly, with FTI. This suggests that total T and the FTI have, if any, very little impact on these parameters and the major determinants must be other factors than androgens. The higher levels of total T and FTI in the group with best self-reported memory compared to the groups with less good memory are confusing but may be explained by the subjectively reported scores. It could also be that sex steroids, i.e. T, have different effects depending on what kind of memory that is analysed<sup>9-11,53</sup>. Cherrier et al.<sup>54</sup> found that T given with an aromatase inhibitor improved spatial memory but not verbal memory, suggesting that in some areas T may act directly and in others T needs to be converted to estradiol to have an effect. In our study different aspects of memory were not taken into account and that may be the reason why the results are somewhat contradictory. Total T and FTI showed no correlation with sleep, health and sexual well-being and this supports results from another study<sup>7</sup> but is in contrast with a study that found that women with lower sexual well-being had lower total T and free T concentrations<sup>6</sup>. In yet another study, total T concentrations positively correlated with orgasmic capacity in postmenopausal women<sup>55</sup>. The differences may be explained by the way questions are asked and how specific or broad the questions are. In our study the women were asked to rank their sexual well-being on a seven score scale. Female sexuality has many aspects and is affected by different factors, which may explain the various results. Maybe questions on different aspects of sexual life should have been asked instead of one broad question to be able to better discriminate between different aspects of the sexual well-being and their relations to androgen levels. We have no explanation to the slight albeit significant association between FTI and symptoms like dizziness, impaired hearing and joint problems.

The lower SHBG levels in the PMO group compared to the PM group are in accordance with some studies<sup>23,26,29</sup>, but not with others<sup>28,30,31</sup>. BMI and WHR were negatively correlated to SHBG and the regression analysis showed that the SHBG levels could partly be explained by the BMI and WHR. This is supported by other studies<sup>20-22</sup>. It has been proposed that increasing BMI is associated with a rise in insulin levels, which in turn inhibit the liver synthesis of SHBG<sup>21,56,57</sup>. Estradiol had a positive impact on the SHBG levels and even though both age (positively) and T (negatively) were significantly related to the SHBG levels when all women were included in the analysis, their contribution was very small. T has previously been reported to be negatively correlated to SHBG in postmenopausal women<sup>21</sup> even though the opposite has also been reported<sup>28</sup>.

The higher frequency of estrogen-related symptoms, hot flushes and vaginal dryness<sup>52</sup>, in the PMT- and PMO-groups is probably associated with the normal menopausal transition.

It is surprising that women on HRT reported more current flushes than the other women. In the questionnaire it was asked for current existing hot flushes. It might be that some of these women misunderstood the question and reported flushes since that was the cause of taking HRT even though they did not have flushes at the moment when filling in the questionnaire. Otherwise, the effect of HRT used in these women was not sufficient. The higher prevalence of vaginal dryness in the PMO group is in accordance with earlier reports, implying that the menopausal transition with falling estrogen levels has an effect on the vaginal mucosa and that HRT probably ameliorates these symptoms<sup>58</sup>.

The women on HRT reported less satisfaction with mood and energy than the two other groups studied. The women using HRT also had lower memory scores compared to the PMO group. Sleep, health and sexual well-being were better in the premenopausal group than in the other groups suggesting that the menopausal transition has negative effects on these aspects of

life. The higher scores on sexual well-being in the PMT group compared to the PMO group may be explained by the higher frequency of vaginal dryness in the PMO group.

In summary, we found that lower T concentrations were associated with some aspects of lower quality of life in perimenopausal women but not to sexual well-being. The significant differences in androgens that were found in some of the analyses were small and the biological relevancy of the differences is questionable. There must be other factors than decrements in sex hormones that contribute to the emergence of some perimenopausal symptoms. Further studies are needed to find causes and mechanisms that explain the complex symptoms related to the menopausal transition and what role androgens may play in the emergence of menopausal symptoms.

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