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**Vasomotor symptoms usually reappear after cessation of postmenopausal hormone therapy – a Swedish population based study.**

**Running title: Recurrence of vasomotor symptoms after HT**

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**Abstract** (218 words)

*Objective:* To investigate to what extent vasomotor symptoms reappeared after cessation of postmenopausal hormone therapy (HT) in women who started HT due to hot flashes.

*Design:* A cross-sectional postal survey. A validated questionnaire was sent to all women, 53-54 years old, living in Linköping, Sweden (n=1,733) including questions about menopause, HT and vasomotor symptoms. Pearsons chi-square test and logistic regression were used for statistical analyses.

*Results:* Response rate after one reminder was 77.3 %. After omitting incomplete answers 72.9 % remained for analysis. In all 319 (25.3 %) women were current users of HT, 242 (19.2 %) previous users and 702 (55.6 %) were never users. Of the 242 previous users 165 (69 %) women stated that they had vasomotor symptoms before starting HT. Vasomotor symptoms recurred after cessation of HT in 143 of these 165 women (87 %). We found no significant difference in symptom recurrence in comparisons of the three groups based on usage of HT for 0-1, 2-4 or 5 years or more.

*Conclusions:* The majority of women who had vasomotor symptoms when they initiated HT reported recurrence of symptoms after cessation of HT (87 %), although the flashes were usually reported to be less frequent and bothersome than before HT. Effective and safe treatment approaches for women with recurrence of vasomotor symptoms are needed.

**Key words:** climacteric, hormone therapy, menopause, discontinuation of hormone therapy, recurrence of vasomotor symptoms, cessation of treatment

## Introduction

Menopause is defined as the last menstrual bleeding and occurs in women from the Western world around age 51<sup>1</sup>. Vasomotor symptoms such as hot flashes and sweating are reported in up to 75% of women around menopause<sup>2</sup> and often affect night sleep and quality of life. Hormone therapy (HT) usually estrogen combined with progestagens effectively decreases vasomotor symptoms. The use of HT increased rapidly during the last decades of the 20<sup>th</sup> century and about 45 % of peri- and postmenopausal women used HT in our area in 1998<sup>3</sup>. The increase in HT usage was probably a consequence of the results from several observational studies that indicated benefits of long-term use of HT on vasomotor symptoms, cardiovascular risk, osteoporosis and fracture risk, colon cancer and Alzheimer's disease<sup>4-6</sup>. However, results from more recent larger, prospective, and randomized clinical trials could not find evidence for primary (WHI-study<sup>7</sup>) or secondary (HERS-study<sup>8</sup>) preventive effects of HT on cardiovascular risks in the age groups studied. In addition, the Million Women Study<sup>9</sup> found and confirmed an increased risk of breast cancer associated with long-term use of HT. In the years after these results were published, the use of HT has decreased dramatically in Sweden<sup>10, 11</sup> and in several other countries as well<sup>12-15</sup> indicating that fewer women start HT and more women are stopping HT. A number of mainly retrospective studies have tried to establish to what extent vasomotor symptoms recur after HT has been abandoned<sup>16-18</sup>. Most of these studies have, however, not distinguished between the primary reasons for use of HT and consequently they have not identified those women who had started HT due to hot flashes.

A few years after the WHI study was published the concept of the "window of opportunity" was launched, suggesting that the risk- benefit profile depends on when, in a woman's reproductive life, HT is initiated. Thus, a reanalysis of the WHI-data with meta-analysis of observational and

randomized controlled trial data by age of initiation of therapy suggests that, when HT is started within 4-6 years of menopause, there is cardio- and neuro-protection<sup>19</sup>. Nevertheless, many women try to abandon HT<sup>10</sup> and it is important therefore to study the risk of symptom recurrence in order to provide better counselling of women before and during HT use.

The objective of this study was to investigate to what extent vasomotor symptoms reappeared after cessation of postmenopausal HT in women who once started HT due to hot flashes. We also intended to identify possible background factors that might have contributed to women's decision to abandon HT.

## Methods

The study was a cross sectional questionnaire trial involving two age-cohorts in Linköping, Sweden. We used a questionnaire regarding women's attitudes and knowledge about menopause and hormone therapy as well as background data (such as education, language, area of residence, marital status, employment, and smoking habits), current and previous use of HT, if they had vasomotor symptoms before HT was started, present vasomotor symptoms, reasons for discontinuing HT etc. The questionnaire was mailed to the total population of women (n=1,733) aged 53 and 54 years living in the community of Linköping in the second quarter of 2003. The local population authorities provided the names and addresses.

This questionnaire was developed from a questionnaire originally validated in several steps and used in 1999 in a similar population<sup>10</sup>. An almost identical version was used in 2003 with the addition of a separately validated section with questions about knowledge of reproductive physiology, which has been reported separately<sup>20</sup>.

Use of HT was defined as current or previous use of oral or transdermal HT but excluded local or oral estriol treatment for urogenital discomfort. Never-users were women who had never used HT for climacteric or other symptoms. Education level was assessed in three categories; 9 years compulsory school, 12 years upper secondary school, and university degree or other education for at total of at least 15 years.

*Data handling and statistics:* The questionnaires were coded, which enabled us to send a reminder to women who had not answered after four weeks. The returned questionnaires, except for the identifying code, were optically scanned into the computer and analyzed using SPSS for Windows (release 14.0.0).

The agreement between optical and manual reading was checked for the first ten complete questionnaires and the optical reading was continued only after the manual and optical reading agreed totally.

Pearson chi-square test was used to analyse differences between groups. Logistic regression was used in order to analyse association between background factors (education, language, area of residence, marital status, employment, and smoking habits) and proneness to abandon HT. The p-value was set to  $<0.05$  (two-tailed) to be considered significant.

*Ethics:* The local ethics committee at the Faculty of Health Sciences, Linköping University, approved the study design, including the questionnaire.

## Results

After one reminder 1,339 of the 1,733 (77 %) questionnaires were returned. Several questions were related to current or previous HT use from different perspectives, which enabled us to exclude women who did not answer these questions consistently. In a similar way we excluded women who gave inconsistent answers to two questions concerning their menopausal status. This left us with a final analyzable rate of 1,263 of the 1,733 mailed questionnaires; i.e. a 73 % rate of analyzable questionnaires. Not all questionnaires were completely answered and 0.5-2.7 % of the answers to the separate questions were missing.

Demographic data are presented in table 1. Educational level appeared to be evenly distributed between the three levels of education (nine-year compulsory school = 31.6 %, upper secondary school = 30.4 %, university degree or equivalent in time = 37.4 %). Five percent of the women stated that their first language was not a Scandinavian language (Swedish and the closely related Norwegian and Danish). According to data from the local population authorities, 9 % of women in Linköping age 53 to 54 in 2003 had immigrated to Sweden from countries outside the Nordic region. Rural women were more common in the group of previous users than among current users ( $p=0.002$ ).

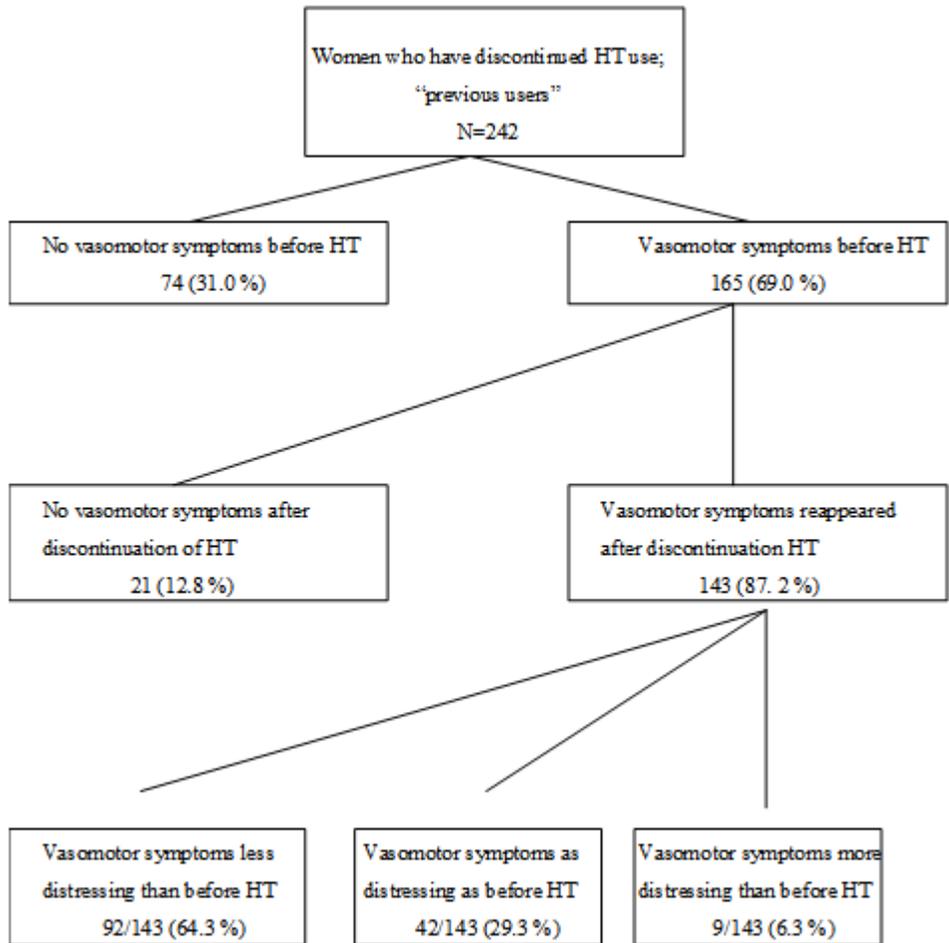
Figure 1 summarizes the results referring to possible recurrence of vasomotor symptoms after cessation of HT. In all, 319 (25.3 %) women were current users of HT, 242 (19.2 %) previous users and 702 (55.6 %) were never-users. Data on previous HT users' preparations were not asked for in the questionnaire. About 17 % of the current users reported transdermal regimens and the remaining current users reported oral route of HT. About half of the oral preparations were sequential regimens and the other half continuous combined or only estrogens in hysterectomized women. The dose was usually 1 or sometimes 2 mg  $17\beta$ -estradiol or 0.625 mg conjugated estrogens per day and about 5% used tibolone.

**Table 1** Demographic data on current and previous users of hormone therapy (HT).

<u>Back-ground variables</u>	<u>Current HT users</u>		<u>Previous HT users</u>		<u>P-value*</u>
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	
<i>Education</i>					
9 years compulsory school,	110	34.6	75	31.1	0.54
12 years upper secondary school	99	31.1	73	30.3	
University level	109	34.3	93	38.6	
Total	318		241		
<i>Language</i>					
Swedish	307	96.2	229	95.0	0.06
other Scandinavian	6	1.9	1	0.4	
outside Scandinavia	6	1.9	11	4.6	
Total	319		241		
<i>Smoking</i>					
Yes	73	22.9	48	19.8	0.38
No	246	77.1	194	80.2	
Total	319		242		
<i>Area of residence</i>					
Urban	283	88.7	191	79.3	0.002
Rural	36	11.3	50	20.7	
Total	319		241		
<i>Employment</i>					
Full- or part time	263	82.4	183	75.6	0.21
Housewife	2	0.6	1	0.4	
Sick leave/sick pension	47	14.7	49	20.2	
Student/unemployed	7	2.2	9	3.7	
Total	319		242		
<i>Marital status</i>					
Married/ living together with partner	235	73.7	185	76.4	0.69
Unmarried, living alone	56	17.6	40	16.5	
Living alone but having a partner	28	8.8	17	7.0	
Total	319		242		

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\* P-value analysed with Pearson's chi-square test



*Figure 1: Vasomotor symptoms before and after use of hormone therapy (HT) in women who have abandoned hormone therapy.*

Of the 242 previous users 143 (59 %) had discontinued HT within the last 2 years and 165 (69 %) women stated that they had vasomotor symptoms before starting HT. Vasomotor symptoms recurred after cessation of HT in 143 of the 165 women (87 %) who had experienced symptoms when they once started HT, although for most of them symptoms were reported to be less distressing than before the start of HT (Fig 1). We did not find any significant difference in symptom recurrence between the women in the three groups who had used HT 0-1, 2-4 or 5 years or more. In addition, a comparison of the frequency of symptom recurrence in the group that used HT for up to two years with those who had used HT for more than two years showed no difference ( $p = 0.34$ ).

About every other previous HT user (50 %) had used HT for less than three years. Many women had discontinued HT rather recently; 37 % within the past year, 24 % between one and two years earlier and 39 % more than two years earlier.

The 242 previous users of HT stated the main reason for deciding to discontinue HT. The most common reasons for discontinuation were fear of side effects (81 women; 34 %), doctor's recommendation (42 women; 17 %), the woman's own decision to try without HT (39 women; 16 %), experienced side effects (35 women; 15 %) and other reasons (38 women; 16 %).

The logistic regression analysis examined how background data contributed to women's decision to abandon HT. The analysis showed that women who were rural residents abandoned HT to a greater extent than urban women ( $p=0.002$ ). No other background factor was related to the tendency to abandon HT and in all the six factors contributed with only about 6 % (Nagelkerke  $R^2 = 0.063$ ).

## Discussion

This study showed that the majority of women (87 %) who had suffered from vasomotor symptoms like hot flashes and sweating when they had once started HT also experienced such symptoms after they had stopped HT. Most women, however, reported that the post-HT symptoms were less bothersome than they had been before HT. We could not find any evidence that the tendency for the symptoms to recur was lower in women who had used HT for a longer time but this result could be due to a lack of power in this study.

It is well known that a number of symptoms may recur after cessation of HT including vasomotor symptoms, psychological symptoms, and local vaginal discomfort<sup>16, 21-22</sup>. Hot flashes and sweating seem to be the symptoms that recur most frequently. In the present study we found a higher rate of recurrence of vasomotor symptoms than has been previously reported. Most previous studies, in contrast to ours, have not specifically identified those women who actually suffered from vasomotor symptoms before HT was initiated, which probably explains this difference. It could be argued that symptoms might still recur in some of the women in our study who had stopped HT very recently, e.g. the 87 women who had stopped within the preceding year. This would, however, lead to an underestimation of recurrence rate in our study. In accordance with our findings, other studies have found that the symptoms were less bothersome after cessation of HT than before initiation of HT<sup>21</sup>, although recall bias might decrease the validity of these findings.

Haimov-Kochmann and coworkers<sup>22</sup> compared recurrence of vasomotor symptoms between women who tapered down or abruptly stopped HT and found that tapering down HT only seemed to postpone the recurrence of symptoms. They suggested that this might support the hypothesis that symptoms recur when estrogen concentrations fall below a certain level, which happens later when HT is tapered down than when HT use is stopped abruptly. The precise mechanisms behind the

reappearance or subsequent disappearance of vasomotor symptoms are still unknown but probably are related to changes in neurotransmitter concentrations in cerebral areas involved in thermoregulation<sup>23</sup>. No studies have shown that the actual recurrence rate of vasomotor symptoms is lower after tapering down of HT compared to abrupt cessation, although most studies are retrospective. One advantage with tapering down HT may be that this method enables identification of the lowest possible dose that will prevent symptoms from appearing.

Factors like genetics, life style factors such as smoking, diet and exercise habits, socio-economical factors, and Body Mass Index might affect the risk to have hot flashes and probably also the risk of recurrence of flashes<sup>24</sup>. However, in this study such factors were not measured and could therefore not be analyzed.

We have previously found that about 40 % of women of the same age as our study group used HT in 1999<sup>10</sup> and thus HT use has dropped to almost half within the five years between 1999 and 2003, probably partially as a consequence of the reporting of the WHI-study<sup>7</sup>. Of those women who had ceased HT in our study 37% had done so within the preceding year and therefore after publication of and media reporting about the WHI study. This is in accordance with other studies showing major reduction in HT use after the WHI data<sup>14, 25</sup> were published. Women who had originally started HT in the belief that it would have preventive health effects stopped HT to a greater extent than those who had originally started because they were experiencing symptoms<sup>14</sup>. The reasons for abandoning HT were similar to those found in previous studies: side effects, recommendations from a doctor, fear of cancer, and long term HT<sup>20, 26, 27</sup>. Li and co-workers reported that background factors such as education and employment contributed to the women's decision to abandon HT or not<sup>27</sup>.

We could only find that area of residence predicted women's propensity to abandon HT, for which we have no explanation.

A high response rate is essential for a questionnaire study. Our response rate of 77%, of which we analyzed 73 % after omitting answers with inconsistent results, is in accordance with other previous Swedish questionnaire studies<sup>2, 10, 20</sup>, and above the recommended minimal response rate of 65%<sup>28</sup>. The method of asking about HT use in several different ways and then excluding the women who answered inconsistently strengthened the study by increasing its internal validity. In addition, we made a test-retest analysis of a number of the questions and found that for almost all questions women ticked the same box or just moved one step in any direction the second time<sup>20</sup>. This suggests that the women did not answer at random, but actively tried to identify the box that suits best their belief and knowledge. However, many of the questions in the questionnaire concerned historical data which may make them less valid.

A weakness in our study is the fact that it did not include a group of immigrant women proportional to the present percentage of immigrants in Sweden. The studied community has a relatively small immigrant population, and an even smaller population of immigrant women who have reached postmenopausal age. Moreover the drop-out rate due to linguistic problems was probably higher among women born outside than those born within Sweden and Scandinavia. Therefore our conclusions are mainly based on non-immigrant women.

It could have been advantageous to have included a wider age range of women, making the results more general. Since we also asked other questions we, however, decided to ask women quite short time after median menopausal age, who probably recently or currently had to consider those questions asked for. Furthermore the age group chosen probably includes women currently recommended to use short time HT due to moderate or severe climacteric symptoms and also a number of women who had used HT for a number of years and were recommended to try to abandon HT. A shorter time since menopause should also make data more valid and reduce recall bias.

In conclusion we found that the majority of women who had suffered from vasomotor symptoms like hot flashes and sweating when they once had started HT also experienced such symptoms after they abandoned HT. Most women, however, reported that the post-HT vasomotor symptoms were less bothersome than the pre-HT symptoms. This is of importance for health care providers when counselling women before and during HT use. Furthermore, the “window of opportunity” concept has to be extended, in order to shed light not only on the importance of starting HT during the optimal time period of a woman’s reproductive life but also on the risk-benefit relationship when such therapy is prolonged and not simply given for the shortest possible time period. Effective and safe treatment approaches for women with recurring vasomotor symptoms are needed, whether that is HT or alternatives to HT.

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