Author’s response to reviews

Title: Postmenopausal hormones and sleep quality in the elderly: a population based study

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Author’s response to reviews: see over
Dear Dr. Norton:

We are pleased to submit responses to reviewer comments for our manuscript, “Postmenopausal hormones and sleep quality in the elderly: a population based study”. We appreciate the reviewers’ comments and suggestions for revisions and believe the manuscript to be stronger with these changes. Each comment is shown in bold italics, followed by our response. In the text of the revised manuscript we indicate the changes by underlining the updated section.

Referee 1:

Abstract

In results section please mention that actigraphy measurements were performed for approximately half of the original sample.

Percentages are now reported in the abstract (page 2).

Introduction

There are several different expressions concerning sleep quality in second paragraph, page 3. However, the word ‘quality’ is not found anywhere, only ‘sleep architecture’ and other versions. Please specify definition of sleep quality in this case.

We now specify sleep quality in terms of total sleep time, sleep efficiency, number of awakenings, wake after sleep onset, and sleep latency (page 3).

The references 7 and 28 including conflicting results on sleep quality are not described- what were the parameters studied in them and why did they not agree with other studies?

Now references 7 and 29. We elaborate on the results that estrogen alone, but not estrogen plus progestin, alleviated the frequency of nocturnal movement arousals (page 3).

The data base or methods used in measurements do not belong to the introduction, please delete and concentrate on hypothesis and aims of the study.

Methods have been removed from the introduction.

Material and methods

How many women were excluded in the primary stage due to hip replacement or walking problems?

Since not having a hip replacement or walking problems was a requirement for entering the SOF study we do not have these numbers available (these participants were not included). The numbers given in the methods reflect the entire study after these exclusions.
It seems that there were no information available from sleep in the baseline questionnaires? Please specify.

Correct, we do not have a baseline sleep questionnaire.

For how long current users had used HT? How long time approximately past users had from their last use?

80% of current users had used HT for >5 years and 90% had used for >3 years. 65% of past users stopped using HT >5 years prior to the sleep visit. The remaining participants had stopped HT use ≤ 5 years prior to this study. These numbers are now indicated in the manuscript (Pages 5-6).

Please give a reference to Sleep-watch-O validation study, now lacking from reference list.

The reference is now included.

How large proportion of women were consistent HT users and how many inconsistent?

Among the 1713 HT users in this study, 1410 used HT consistently and 303 stopped and restarted HT use.

Physical activity was assessed by asking the number of blocks walked daily. Is it possible that there might be persons living in other surroundings without blocks- were there many missing responses for this question?

We also asked whether women walked for exercise (yes/no) which was similarly associated with the three HT levels (see Table 1). We adjusted for this variable in place of ‘number of blocks walked’ and the results do not change. We prefer to use ‘number of blocks walked’ in our analysis because it is more quantitative than the binary (yes/no) covariate.

In page 6, last lines it is mentioned that adjusted means of the sleep parameters were analyzed. However, in page 5, 3rd paragraph it is mentioned that parameters were analyzed as categorical.

Both continuous and categorical measures were analyzed. This is now clearly indicated in the methods section (pages 6-7).

Results

In the first paragraph, 4th line- how much higher prevalence non-measured sample had several health conditions? Please specify which conditions they had.

Those without actigraphy had higher rates of IADL impairment and stroke, a worse mean depression score, lower cognitive functioning, and were more likely to be diagnosed with Alzheimer’s disease (page 8).

Since the mean age of the women was considerable high (84 years), the term ‘elderly’ could be changed to a more descriptive word

We have found that the term ‘elderly’ is most preferred both by the Study of Osteoporotic Fractures investigators and by the journals publishing our results. Using ‘elderly’ will help us maintain consistency among publications.
In the second paragraph, on 9th line is written that current and past users of HT were more likely diagnosed with depression compared to never users. However, on Table 1 in GDS Score or antidepressant use there were very small differences between groups, not supporting this finding?

Table 1 now includes data on whether participants were ever diagnosed with depression. Current HT users had lower rates (8.81%) compared with past (14.35%) and never users (15.13%) (P<.0001).

Discussion

In the first paragraph the current study is told to be the first to evaluate sleep characteristics and long-term HT. However, later in the same paragraph the authors mention that majority of studies consider menopausal transition and sleep- but minority may overlap with this study age-group?

It is true that the majority of studies focus on the menopausal transition. We believe that the current study is important because the focus is on postmenopausal women (77-99 years). The reference to studies of the menopausal transition has been cut back and is only used to demonstrate the paucity of information on women in this older age group.

Conclusions could mention the fact that only two out of five sleep parameters differed by HT status, thus more qualitative or other sleep indicators might also be needed to interpret the significance of the finding.

We indicate in the abstract (page 2) and conclusions (page 12) that two out of five sleep parameters were improved.

Please discuss references 7 and 28 mentioned in the introduction- what were the parameters used in these studies?

We point out in the introduction that estrogen alone, but not estrogen plus progestin, alleviated the frequency of nocturnal movement arousals as measured by polysomnography.

Second paragraph has a long discussion on biological mechanism. Although it is relevant for the proposed associations, it is quite lengthy and should be abridged on the basis that there is no empirical data on receptor level.

The speculative discussion of receptors has been removed (page 10). The discussion is now focused on better established mechanisms.

Page 11, second paragraph, line 6 states that HT information was collected approximately every two years for 16 years time. This could be explained in the methods as well.

These points are now included in the methods section (page 5).

Conclusions

Although limitations are well described in page 11, last paragraph, they are not conveyed to the conclusions stating that HT usage improves sleep quality. Age-group and limitations concerning 2 out of 5 sleep parameters should be mentioned as well.

We indicate in the abstract (page 2) and conclusions (page 12) that two out of five sleep parameters were improved.
The last sentence has as a reference a study describing quality-of-life indicators, although vascular side-effects are discussed. A more appropriate reference considering cardiovascular effects should be found.

We have included several relevant and high impact publications on HT and cardiovascular effects (Page 12).

Referee 2:

Do the authors want to comment on the potential confounding effects of sleep apnea and the findings of Bixler et al AJRCCM 2001, Young et al 2003, Shahar et al AJRCCM 2003 and perhaps Woodward &Freedman SLEEP 1994? The last reference may not be relevant for hot flashes as you state in the discussion. However, the possibility of an HT effect on sleep apnea coupled with the potential problems of interpreting actigraphy when substantial OSA is present (Wang et al J Clin Sleep Med 2008) might be worth a mention?

We realize that the lack of PSG data in this sample of women is a limitation (Page 12). With regard to the potential for sleep apnea to confound our analyses we have included a discussion that addresses the points raised by the reviewer (Pages 10-11). In particular, the combined data in the referenced studies suggest that menopause is a significant risk factor for SDB in women and that HT appears to be associated with reduced risk. However, it should be noted that age and BMI are significant risk factors for SDB and that the inverse relationship between HT and SDB was weakest among the oldest age group ≥70 years, which is similar to the age group in the current study (Pages 10-11). We also take into consideration the actigraphy vs. PSG results for those with substantial OSA (Page 10).

One of the key issues raised by the differences between the clinical cohorts and the clinical trials of HRT was that of uncontrolled confounding by socioeconomic status. When I read that former use of HRT was associated with better sleep this was the first thing I thought of. HRT is associated with higher SES and higher SES people have better sleep and SES is not completely captured by the available education and race measures (particularly for women of this generation education may not have been a measure of SES). Do you want to briefly discuss this potential reason for your findings in the paper?

We performed several analyses to minimize confounding by indication and contraindication, but the possibility of these biases cannot be eliminated without use of a randomized controlled trial design. Years of education, a proxy for socioeconomic status, differed between never and past/current HT users but was not related to the likelihood of sleep disturbances in our cohort. We acknowledge in the limitations sections of the discussion that education as a surrogate for SES may be an inadequate measure of SES in this cohort of elderly women (page 12). In addition, we recognize that confounding by unknown factors or factors we were not able to control for in the analysis could also have resulted in biased estimates of effect (page 12).

Thank you for your consideration of our manuscript.

Sincerely,

Gregory Tranah, PhD.