

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Cohort Study of the Association of Hypnotic Use with Mortality in Postmenopausal Women
<b>AUTHORS</b>	Hartz, Arthur ; Ross, John

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Barbara Phillips, MD, MSPH Professor, Division of Pulmonary, Critical Care and Sleep Medicine University of Kentucky College of Medicine Lexington, KY USA  I have no conflicts relevant to this paper.
<b>REVIEW RETURNED</b>	03-May-2012

<b>THE STUDY</b>	<p>This study is the result of a secondary analysis of data relating to hypnotic use, sleep disturbance, and mortality in the Women's Health Initiative. The cohort is large and the time of follow-up (8 years) is relatively long. There are several interesting findings, including confirmation of the association between regular hypnotic use and unhealthy lifestyle, as well as mortality. The authors also noted no increased risk of death for those with "sleep disturbances" but increased risk of death for long (&gt;10 hours/night) sleepers. Their paper is well-written.</p> <p>Comments/Queries/Suggestions</p> <ol style="list-style-type: none"> <li>1. After confirming multiple other studies demonstrating an association between hypnotic use and death, the authors conclude the abstract and the discussion with the sentence, "It is unlikely that the hypnotics most commonly used in the 1990's contributed substantially to mortality risk." I would consider deleting that sentence. It sounds biased. Indeed, based on their findings that regular hypnotic use is associated with death but "sleep disturbance" is not, one might conclude that the risk of sleeping pills appears much greater than the risk of insomnia. That sounds biased, too. The truth is probably somewhere in between.</li> <li>2. Use of the term "sleep disorders" (which includes everything from bedwetting to tooth grinding to life-threatening sleep apnea) is imprecise and irritating. This term needs to be eliminated from this paper wherever possible, starting with the first paragraph in the introduction.</li> <li>3. There is another recent excellent report of the association between hypnotic use and cancer that the authors might choose to reference (Kao C-H, Sun L-M, Liang J-A, et al. Relationship of</li> </ol>
------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

	<p>zolpidem and cancer risk: a Taiwanese population-based cohort study. Mayo Clin Proc. 2012;87(5):430-436.)</p> <p>4. Last sentence in intro: "...evidence that hypnotic use may increase the risk..." might be changed to "is associated with increased risk."</p> <p>5. HRT use is well-documented in the WHI. In this study, were there associations between HRT, sleep complaints, use of hypnotics?</p> <p>6. The authors excluded some WHI participants from analysis because they "would have been excluded from randomized controlled trials." This seems reasonable. For example, they excluded those with a BMI less than 18. Women with BMI's over 35 to 40 are likely to have had significant sleep-disordered breathing. Vozoris has suggested that this accounts for some of the mortality associate with hypnotic use. (Vozoris NT, Leung RS. Sedative medication use: prevalence, risk factors, and associations with body mass index using population-level data. Sleep. 2011;34(7):869-874.) Should heavy women have been excluded, too?</p> <p>7. Region of the country is associated with mortality (Table 2)? I know it's off the subject here, but the curious reader wants to know WHICH region of the US is most deadly?</p> <p>8. The association between very long sleep and death is interesting, in view of a current report which has been twisted by the media to suggest that long sleep can make one lose weight. (Watson NF; Harden KP; Buchwald D; Vitiello MV; Pack AI; Weigle DS; Goldberg J. Sleep duration and body mass index in twins: a gene-environment interaction. SLEEP 2012;35(5):597-603.) This might be discussed.</p> <p>9. Similarly, this study appears not to have shown an association between short (5 or less hours) of sleep and adverse outcomes. This needs to be discussed.</p>
--	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>REVIEWER</b>	Justin Stebbing Professor of Cancer Medicine Imperial College, London
<b>REVIEW RETURNED</b>	12-Jul-2012

<b>THE STUDY</b>	The English style is poor on the whole and needs revision. The quality of these data and size of the database is high, and the poor English detracts from the excellent findings herein. The use of adjectives is liberal and should be reduced.
<b>GENERAL COMMENTS</b>	This is a very solid study, limited by the textual descriptions, but the data are very strong.

### VERSION 1 – AUTHOR RESPONSE

Reviewer: Barbara Phillips, MD, MSPH

This study is the result of a secondary analysis of data relating to hypnotic use, sleep disturbance, and mortality in the Women's Health Initiative. The cohort is large and the time of follow-up (8 years) is relatively long. There are several interesting findings, including confirmation of the association between regular hypnotic use and unhealthy lifestyle, as well as mortality. The authors also noted no increased risk of death for those with "sleep disturbances" but increased risk of death for long (>10 hours/night) sleepers. Their paper is well-written.

## Comments/Queries/Suggestions

1. After confirming multiple other studies demonstrating an association between hypnotic use and death, the authors conclude the abstract and the discussion with the sentence, "It is unlikely that the hypnotics most commonly used in the 1990's contributed substantially to mortality risk." I would consider deleting that sentence. It sounds biased. Indeed, based on their findings that regular hypnotic use is associated with death but "sleep disturbance" is not, one might conclude that the risk of sleeping pills appears much greater than the risk of insomnia. That sounds biased, too. The truth is probably somewhere in between.

We agree that hypnotic use is associated with subsequent mortality. Our findings suggest that an important reason for this association is that hypnotic use is associated with poor health. After taking into account a few simple measures of poor health, most of the association between hypnotic use and mortality has been removed. We have softened our conclusion based on our findings to read as follows: "This study did not support a strong association of the hypnotics most commonly used in the 1990's with mortality." We revised many parts of the manuscript to justify and clarify this view.

2. Use of the term "sleep disorders" (which includes everything from bedwetting to tooth grinding to life-threatening sleep apnea) is imprecise and irritating. This term needs to be eliminated from this paper wherever possible, starting with the first paragraph in the introduction.

The term "sleep disorders" was replaced with the term "difficulty sleeping".

3. There is another recent excellent report of the association between hypnotic use and cancer that the authors might chose to reference (Kao C-H, Sun L-M, Liang J-A, et al. Relationship of zolpidem and cancer risk: a Taiwanese population-based cohort study. *Mayo Clin Proc.* 2012;87(5):430-436.)

We appreciated this reference and have included it in both the introduction and discussion.

4. Last sentence in intro: "...evidence that hypnotic use may increase the risk..." might be changed to "is associated with increased risk."

We made the change to the abstract as suggested by the reviewer.

5. HRT use is well-documented in the WHI. In this study, were there associations between HRT, sleep complaints, use of hypnotics?

We now report that there were statistically significant associations between frequent hypnotic use and difficulties sleeping although the correlations were perhaps lower than expected: 0.20 for difficulty initiating sleep, -0.12 for quality of sleep, and -0.01 with number of hours of sleep. We did not report the correlations of HRT use with difficulty sleeping, -0.01, or with sleep complaints, 0.05, because these relationships were outside the scope of this manuscript.

6. The authors excluded some WHI participants from analysis because they "would have been excluded from randomized controlled trials." This seems reasonable. For example, they excluded those with a BMI less than 18. Women with BMI's over 35 to 40 are likely to have had significant sleep-disordered breathing. Vozoris has suggested that this accounts for some of the mortality associate with hypnotic use. (Vozoris NT, Leung RS. Sedative medication use: prevalence, risk factors, and associations with body mass index using population-level data. *Sleep.* 2011;34(7):869-874.) Should heavy women have been excluded, too?

Valoris hypothesis makes sense, and we were able to test it in our database. We report that our findings did not support his hypothesis.

7. Region of the country is associated with mortality (Table 2)? I know it's off the subject here, but the curious reader wants to know WHICH region of the US is most deadly?

The only region with a significantly elevated mortality rate was the West, which had a rate 10% higher than the Northeast after adjusting for the other covariables. We did not include this finding in the manuscript, because it raises a complex issue that is outside the scope of this manuscript.

8. The association between very long sleep and death is interesting, in view of a current report which has been twisted by the media to suggest that long sleep can make one lose weight. (Watson NF; Harden KP; Buchwald D; Vitiello MV; Pack AI; Weigle DS; Goldberg J. Sleep duration and body mass index in twins: a gene-environment interaction. SLEEP 2012;35(5):597-603.) This might be discussed.

I reviewed the paper suggested by the reviewer, and I agree that the media has greatly misinterpreted the results. I hope that the clear results in this study will suppress any talk about the value of sleeping more than 10 hours a night.

9. Similarly, this study appears not to have shown an association between short (5 or less hours) of sleep and adverse outcomes. This needs to be discussed.

We added a sentence saying that there was an association between very short sleep and subsequent mortality although this association appeared to be removed after adjusting for other risk factors. Perhaps some mortality risk factors contributed to very short sleep.

Reviewer: Justin Stebbing

The English style is poor on the whole and needs revision. The quality of these data and size of the database is high, and the poor English detracts from the excellent findings herein. The use of adjectives is liberal and should be reduced.

The article has been extensively revised for clarity.