Author's response to reviews

Title: Rotating night shifts too fast may cause anxiety, decreased attention performance and may impact prolactin levels during the daytime after night shifts- a case control study

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Author's response to reviews: see over
Covering letter

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1. The manuscript of “Rotating night shifts too fast may cause anxiety, decreased attention performance and may impact prolactin levels during the daytime after night shifts- a case control study” submitted to “BMC psychiatry” has not been published or submitted for publication elsewhere and has been approved by each author.

2. Written informed consents were obtained from all patients prior to participation in the study, which was conducted with the approval of the Ethical Committee of Kaohsiung Municipal Kai-Syuan Psychiatric Hospital. The statement appear in the Method section line131-134.

3. There were no conflicts of interest for all authors.

4. All authors have contributed significantly and are in agreement with the content of the manuscript.

5. We gave point-by-point response to the reviewers concerns.

Authors: Yu-San Chang
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Dear Editorial Office:
The Manuscript No. 1524847311126174 entitled “Rotating night shifts too fast may cause anxiety, decreased attention performance and may impact prolactin levels during the daytime after night shifts - a case control study” which was previously submitted to the BMC Psychiatry has been revised. The reply to the comments of reviewers sees below.

Reply to Reviewer 1 comments
Introduction:
Comment 1. page 1 line 84:not sure what this is. not everyone is familiar with this rotation system. How is it helpful to the circadian rhythm? this section needs more to help the reader understand the distinctions among this system and other systems.
Reply: We revised the introduction and methods are bellowed:
1) Background section, p. 4, line 79-85 "Shift work schedules in the medical field vary depending on a variety of conditions, including length of work hours (e.g. 8-h shifts or 12-h shifts), fixed or rotating scheduling, and duration of rotation. A slower rotation permits a worker to gradually adjust their circadian rhythm over a period of two to four weeks [1]. In faster rotation (shifting every three to five days), it is assumed that workers will maintain constant circadian rhythms in co-ordination with the environment [1]. A 8-h shift system with faster rotation is common in the medical field in Taiwan."

2) Methods section, p. 6, line 120-125 "Most of the work schedules of our nurses consist of repetitive blocks of two consecutive day shifts (8 a.m. to 4 p.m. or 8 a.m. to 5:30 p.m.), two evening shifts (4 p.m. to 12 a.m.), two night shifts (12 a.m. to 8 a.m.), and then at least one day off. Occasionally, nurses work night shifts for three to four days consecutively due to manpower demands. “

Comment 2. The authors mention assaying biomarkers but there is no rationale for them in the intro.
Comment 3. Additional material is needed to bolster why this topic is important and the literature to support it.
Reply: We revised the introduction are bellowed:

   Background section, p. 4, line 96-105 “In addition, sleep deprivation has also been reported to have an impact on sleep-related hormones. Leproult et al. [3] reported that sleep
loss appears to delay the normal return to evening quiescence of the corticotropic axis, resulting in increased cortisol levels the following evening compared with the previous evening. Sleep deprivation has also been reported to result in an increase in thyrotropin (TSH) levels to about double the usual level [4]. However, little is known about the impact on sleep-related hormones during the daytime after working different lengths of consecutive night shifts. This is an important area of research that can provide valuable information regarding physiological changes after consecutive night shifts.”

Methods:
Comment 1. page 6 line 110 this does not make sense?
Reply: We revised the methods are bellowed:
Methods section, p. 6, line 120-125 “Most of the work schedules of our nurses consist of repetitive blocks of two consecutive day shifts (8 a.m. to 4 p.m. or 8 a.m. to 5:30 p.m.), two evening shifts (4 p.m. to 12 a.m.), two night shifts (12 a.m. to 8 a.m.), and then at least one day off. Occasionally, nurses work night shifts for three to four days consecutively due to manpower demands. To prevent adaption to night shifts, all of the nurses had worked either day time shifts or been free of duty for at least three days before entering the study.”

Comment 2. page 9 line 159 The MWT was administered as per the modified 160 MSLT, need more for the assays. How senstitive, how much could be measured, how was blood taken etc.
Reply: We revised the methods-measurements are bellowed:
Methods-measurements, p. 9, line 177-179 “The MWT was administered in a similar method as the MSLT. The major differences were that in the MWT the subjects were instructed to remain awake, and the termination criterion was 40 minutes. “
Methods-measurements, p. 9, line 180-183 “Blood samples were collected by venipuncture (5 ml) in vacuum tubes for sleep-related hormone assays. Serum was separated immediately after blood collection, and the samples were stored at -20°C until analysis. Quantitative determination of cortisol, PRL, GH, and TSH levels in the serum were...” p. 9, line 189-191 “The lower limits of detection were 0.4 ug/dl, 0.16 ng/ml, 0.01 ng/ml, and 0.0025 mIU/L, respectively.”
Comment 3. In the discussion there is no "discussion" about the biomarkers. You restate that they did not differ/or did but there is no talk about why they are important

Reply: We revised the discussion are bellowed:

p. 15, line 299-307 “Cortisol release is mainly controlled by the circadian rhythm which peaks in the early morning and declines throughout the daytime to a nadir in the late evening [4]. It has been reported that experiencing sleep deprivation the previous day would not affect circadian rhythm-related cortisol release [22]. TSH is regulated by both sleep and the circadian rhythm, and the level is low during the daytime with a gradual increase in levels towards the evening reaching a maximum just prior to the onset of sleep [4]. Sleep deprivation causes an elevation of nocturnal TSH level, and this elevated TSH level persists during the daytime because of the prolonged half-life of this hormone [23].”

p. 16, line 308-315 “In this study, the subjects in the night shift groups experienced sleep deprivation before the test day which would not affect circadian rhythm-related cortisol release. However, some studies have reported an elevation in evening cortisol levels compared to controls either under chronic sleep deprivation [24, 25] or acute sleep loss [3]. In addition, stress has been associated with activation of the hypothalamic-pituitary-adrenal axis, and cortisol releasing hormone and cortisol, products of the hypothalamus and the adrenal glands, respectively, are known to cause arousal and sleeplessness [26].... “

Comment 4. statistical section is weak. Needs to include more about covariates (if any) etc.

Reply: We did not include covariate variables in statistical analysis because there was comparable age, years of education, and trait anxiety scores among the three groups.

Comment 5. Quality of written English: Needs some language corrections before being published

Reply: The English has also been checked by a native English speaker. The certification is bellowed:

In addition, we revised sentences in the abstract. p. 2, line 41-42 “We investigated the circadian changes and effects on mood, sleep-related hormone and cognitive performance...”p. 53 “ .... and higher thyrotropin levels than those...”
Title:

Rotating night shifts too fast may cause anxiety, decreased attention performance and may impact prolactin levels during the daytime after night shifts - a case control study

Authors: Yu-San Chang, Hsiang-Lan Chen, Yu-Hsuan Wu, Chung-Yao Hsu, Ching-Kuan Liu, Chin Hsu

This is to certify that the document listed above has been edited to the standards of the industry.

Sincerely,
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Reply to Reviewer 2 comments

Comment 1. Have previous studies investigated the influence of similar types of night shifts on the hormonal factors considered in this study? For instance, there is a literature on the influence of night shifts on cortisol. If so, their findings should be described in the background section. If not, a description of why previous research is not applicable to the Taiwanese nursing population would be useful.

Reply: We revised the introduction as bellowed:

Background section, p. 4, line 96-105 “In addition, sleep deprivation has also been reported to have an impact on sleep-related hormones. Leproult et al. [3] reported that sleep loss appears to delay the normal return to evening quiescence of the corticotropic axis, resulting in increased cortisol levels the following evening compared with the previous evening. Sleep deprivation has also been reported to result in an increase in thyrotropin (TSH) levels to about double the usual level [4]. However, little is known about the impact on sleep-related hormones during the daytime after working different lengths of consecutive night shifts. This is an important area of research that can provide valuable information regarding physiological changes after consecutive night shifts.”

Comment 2. Top of p. 6: What is meant by off-duty nurses? Do these nurses ever participate in night shifts or are they day only workers? If they work nights, when was their most recent night shift? What schedule do they work? These questions are important to understanding their role as the 'unexposed' comparison group and needs to be clarified here.

Comment 3. Related to the previous issue, what are the schedules of those nurses working the night shift, specifically, what are the duration of these shifts? What are the start and end times of each shift? Please elaborate in the methods section on this issue.

Reply: We revised the methods as bellowed:

Methods section, p. 6, line 120-125 “Most of the work schedules of our nurses consist of repetitive blocks of two consecutive day shifts (8 a.m. to 4 p.m. or 8 a.m. to 5:30 p.m.), two evening shifts (4 p.m. to 12 a.m.), two night shifts (12 a.m. to 8 a.m.), and then at least one day off. Occasionally, nurses work night shifts for three to four days consecutively due to manpower
demands. To prevent adaption to night shifts, all of the nurses had worked either day time shifts or been free of duty for at least three days before entering the study.”
Besides, we wrote in the sixth limitation p. 17, line 340-342 “Sixth, not all subjects had the same shift work schedule before entering the study, which may also have confounded the results.”
Comment 4. On p. 9 the authors indicate that serum levels of cortisol, prolactin, GH and TSH were measured from blood samples collected at the end of the testing period. At what time of day were these samples collected specifically? Was this consistent for all participants or was their variation in the time of blood sample collection. Given that some of these hormones, specifically cortisol, have a distinct circadian rhythm, this is an important issue to consider as if samples were collected at different times of day for different subjects this could lead to variability in hormone levels as a result of natural differences in circadian phase and not night shift work specifically.

Reply: We revised the methods are bellowed:
   p.7, line 143-146 “The variation in the time of blood sample collection was within 20 minutes for each participant and each collection, which were performed at 11:00 a.m. – 11:20 a.m., 1:00p.m. -1:20 p.m., 3:00 p.m. -3:20 p.m., and 5:00 p.m. – 5:20 p.m.”
Comment 5. At the top of p. 15 the authors state that sleep restriction in daytime following two night shifts may have led to emotional stress and a state of hyperarousal during the daytime, which may be responsible for the elevated stress levels in this group. Why does this effect not occur for those in the four night shift group as well? Is there any evidence of adaptation to night shifts among the group working 4 consecutive nights? This statement needs to consider the other night shift group when using this explanation of the elevated stress levels seen among nurses in the two night shift group.

Reply: We revised the discussion are bellowed:
   p. 14-15, line 274-288 “The nurses in the two night shifts group experienced acute changes in the wake-sleep cycle during the night shifts. Some studies [12-14] have indicated adaptation to night shifts on the fourth day according to improvements in cognitive performance in the nighttime. Accordingly,
destabilization of homeostatic- circadian two-process model of sleep regulation would be more remarkable in the two night shifts group than in the four night shifts group during the daytime after consecutive night shifts. Sleep deprivation studies [2] have shown a diverse impact on cognitive performance as well as on mood due to destabilization of the wake state. Therefore, in our results, the subjects in the two night shifts group had higher state anxiety scale scores than the four night shifts group and showed a persistent anxiety state throughout the daytime. This may be explained by two consecutive night shifts following sleep restriction being more emotionally stressful than four consecutive night shifts following sleep restriction, which resulted in a state of hyperarousal and may have contributed to the decreases both in performance on attention tasks and learning effect [17, 20]."

Comment 6. In the final paragraph on p. 15 (starting at line 284) the authors indicate that sleep deprivation would not influence cortisol release but would impact TSH. A reference for this statement is provided but further explanation in the text is required to explain why this is the case. Given that cortisol is known as a 'stress hormone' this statement requires clarification.

Reply: We revised the discussion as bellowed:

p. 15, line 299-307 “Cortisol release is mainly controlled by the circadian rhythm which peaks in the early morning and declines throughout the daytime to a nadir in the late evening [4]. It has been reported that experiencing sleep deprivation the previous day would not affect circadian rhythm-related cortisol release [22]. TSH is regulated by both sleep and the circadian rhythm, and the level is low during the daytime with a gradual increase in levels towards the evening reaching a maximum just prior to the onset of sleep [4]. Sleep deprivation causes an elevation of nocturnal TSH level, and this elevated TSH level persists during the daytime because of the prolonged half-life of this hormone [23].”

p. 16, line 308-315 “In this study, the subjects in the night shift groups experienced sleep deprivation before the test day which would not affect circadian rhythm-related cortisol release. However, some studies have reported an elevation in evening cortisol levels compared to controls either under chronic sleep deprivation [24, 25] or acute sleep loss [3]. In addition, stress has been associated
with activation of the hypothalamic-pituitary-adrenal axis, and cortisol releasing hormone and cortisol, products of the hypothalamus and the adrenal glands, respectively, are known to cause arousal and sleeplessness [26]…. “

Comment 7. Related to number 5, since cortisol peaks in the early morning upon awakening, is there any risk that the time of day at which cortisol was measured in this study (i.e. not in the early morning) could be masking differences in cortisol production between study groups? This issue should be considered in the discussion.

Reply: We added the limitation is bellowed:

P.17-18, line 342-347 “Seventh, blood sample were not collected in the early morning when cortisol release should be reaching peak level. This could have masked differences in cortisol production among the study groups. This was because our study was designed to evaluate physiological changes during the daytime after working consecutive night shifts and to avoid cortisol concentrations being influenced by an acute effect.”

Comment 8 On p, 17 the authors list several factors (ex. menstrual stage) that could be confounders for cortisol and PRL levels. What effect would you expect these variables to have (i.e. lead to under/over estimates of hormone levels)? The potential effect of unmeasured confounders in this study should be considered more explicitly.

Reply: We revised the fifth limitation are bellowed:

p. 17, line 337-340 “Fifth, we did not use indwelling catheters to avoid discomfort when collecting blood samples, which may have overestimated the cortisol level. Nor did we record the stage of menstrual cycle, which may have under/overestimated the PRL level in the follicular/ovulatory and luteal phases, respectively [27].”

Commet 9. The last sentence in the results section of the abstract reads: 'However, the cortisol level did not consist with anxiety state in the two night shifts group during the daytime after night shifts'. This sentence, specifically the word 'consist' does not make sense. Do the authors mean that there was no relationship between shift type (off duty, two nights, four nights) and cortisol production? This sentence needs to be rephrased to clarify what is meant by this statement. The same issue occurs in the main text of the manuscript on p.17.
Reply: We revised the conclusions and abstract are followed:

p. 18, line 355-360 “Although the two night shifts group had a higher anxiety state than the four night shifts group during the daytime after night shifts, there was no significant difference in cortisol level between the types of shift. It would be interesting to study further the impact of consecutive night shifts on mood and cortisol level during the daytime of sleep restriction.”

p. 2, line 57 “There were no differences in cortisol level between the types of shift.” P.3 line 60-64 “Although the two night shifts group had a higher anxiety state than the four night shifts group during the daytime after night shifts, there were no differences in cortisol level between the types of shift. It would be interesting to study further the impact of consecutive night shifts on mood and cortisol level during the daytime of sleep restriction.

Comment 10. Please add 'MSL' to the list of abbreviations as it is not clearly defined in the manuscript but is used in the text.
Reply: We added the 'MSL' to the list of abbreviations

p. 19, line 365 “MSL, mean sleep latency”

Comment 11. There is a grammatical error in the sentence from lines 251 - 254, specifically 'which is compatible with previous studies reported people frequently underestimated the impact of sleep restriction on cognitive functions' - the word 'that' should be inserted between 'studies' and 'reported'.
Reply: We revised the sentence are bellowed:

p. 13, line 261-263 “which is compatible with previous studies [17, 18] that reported people frequently underestimate the impact of sleep restriction on cognitive function. “

Comment 12. The end of the sentence from lines 265 - 267 on p. 14 also has some grammatical issues, specifically 'and showed a persistent throughout the daytime' does not make sense. Please revise.
Reply: We revised the sentence are bellowed:

p. 14, line 283-284 “..... showed a persistent anxiety state throughout the daytime.”

Comment 13. Three graphs are provided as part of Figure 4. It would be useful (for clarity) to label these as 4a, 4b and 4c so it is clear to which figure they belong. The same for the two graphs in Figure 5.
Reply: We revised Fig. 4, 5 to label 4a, 4b, 4c and 5a, 5b, respectively
and in the main text of the manuscript on p.11 line 219, 222 “(Figure 4 a- c)”, “(Figure 5 a, b)"
Comment 14. Quality of written English: Needs some language corrections before being published.
Reply: The English has also been checked by a native English speaker.
The certification is bellowed:
In addition, we revised sentences in the abstract. p. 2, line 41-42 “We investigated the circadian changes and effects on mood, sleep-related hormone and cognitive performance...” p. 53 “... and higher thyrotropin levels than those...”

Medical Editing Certificate

Title:
Rotating night shifts too fast may cause anxiety, decreased attention performance and may impact prolactin levels during the daytime after night shifts - a case control study

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This is to certify that the document listed above has been edited to the standards of the industry.

Sincerely,
Yours sincerely,
Ching-Kuan Liu