Author's response to reviews

Title: Delayed sleep onset in depressed young people

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Author's response to reviews: see over
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Dear Dr Ritter,

RE: MS: 8684409291132324

Delayed sleep onset in depressed young people’.

Thank you for the opportunity to revise and resubmit this manuscript. Please find attached our revised manuscript with our response to the reviewers detailed comprehensively below. We have taken special care to ensure that the points raised by the reviewers are addressed as adequately as possible.

Reviewer 1:

R1.1. In the introduction, as evening type can partly explain delayed sleep onset, some references on evening type and depression can be added.

Reviewer 1 commented on the potential links between delayed sleep phase and sleep ‘chronotype’; a preference for either morning or evening living. The literature on whether an observed delayed sleep phase is a different concept than an evening type, an extreme version of it or just another way of terming the same phenomenon, is inconsistent (e.g. Lack et al 2009, DOI: http://dx.doi.org/10.2147). However, given this is a common issue, we have made changes to ensure that sleep chronotype is referred to in the introduction and a recommendation for future studies has been included in the discussion.

In the Introduction, we have added three references and the following text changes are highlighted on page 5: “...the individual limits their sleep to match their sleep chronotype: the degree to which a person organises their daily activities in the morning or evening (Kerkhof, 1998)... The evening preference sleep chronotype has been associated with higher levels of depressed mood, conduct problems and hyperactivity (Hasler, Allen, Sharra, Bootzin, & Bernert, 2010; Lange & Randler, 2011).”

In the Discussion, we have included an additional sentence on page 15 and supported this with two references: “Future studies would also benefit from the use of a chronotype questionnaire, such as the Morningness-Eveningness Questionnaire (Horne & Ostberg, 1976) or Munich Chronotype Questionnaire (Roenneberg, Wirz-Justice, & Merrow, 2003).”

The additional references include:

R1.2. In the methods, even if the inclusion procedure was described elsewhere, more information on who assessed the individuals can improve the global understanding.

Although the study protocol is published elsewhere (Purcell et al., 2013) as requested, we have amended both the Sample and Procedure section of the Methods to more comprehensively describe the methodology. The following paragraph has been added into the Methods section, under the heading ‘Procedure’ and is highlighted on page 7: “Using a structured interview, participants were assessed by research assistants who held graduate degrees in psychology. The structured interview consisted of the clinical measures outlined below in Assessment. Research assistants were trained in the use of the structured interview and achieved an interviewer reliability score of at least 0.8 on each of the interviewer-rated clinical measures before recruitment commenced. The research assistants completed the structured interview with each participant before providing an iPad or laptop for the completion of the self-report measures.”

R1.3. What was the distribution of the variables when T-tests were used?

All variables were examined for their distribution. When t-tests were used, Levene’s test for equal variances was not violated, except for the variables ‘age’ and ‘time spent in bed/self-reported sleep duration’; however, this can be attributed to the inclusion criteria and curtailment that was conducted for the sleep questionnaire. T-tests with equal variances were used for all appropriately distributed variables and a sensitivity analysis for age was conducted. To convey the distribution of the variables more clearly, the following sentence was inserted into the Methods section underneath the Analysis section on page 10: “Levene’s tests for equal variances were conducted for the continuous clinical variables, to which none violated any assumptions.”

R1.4. The lack of objective sleep measures (actigraphy, PSG) even in a subgroup of patients can be added in the limitations.

We agree with this suggestion and thank the reviewer for bringing it to our attention. We have added the following sentence into the limitations section of the manuscript on page 15: “The addition of objective
R1.5. The use of circadian questionnaire to assess chronotype could be considered for future studies.

We agree with this suggestion and thank the reviewer for bringing it to our attention. We have added the following sentence into the limitations section of the manuscript on page 15: “Future studies would also benefit from the use of a chronotype questionnaire, such as the Morningness-Eveningness Questionnaire (Horne & Ostberg, 1976) or Munich Chronotype Questionnaire (Roenneberg et al., 2003).”

In response to the comments by Reviewer 2:

R2.1. Methods, Sample, page 6, line 3. It reads "adult phenotype chronic psychiatric disorder". What do you mean by this? It is not commonly used terminology. Please explain. In addition, does "chronic" refer to incomplete remission or persistent reoccurrence? Please clarify.

We apologise for the ambiguity of this terminology. The phrasing “adult phenotype chronic psychiatric disorder” was intended to describe participants who are experiencing a pattern of severe mental illness that had progressed into a distinct psychotic or recurrent mood disorder (such as schizophrenia, bipolar or recurrent major depression) or one that is persistently reoccurring and non-responsive to treatment. In this context, chronic refers to both incomplete remission and persistent reoccurrence of symptoms (Hickie et al., 2013). To clarify this for readers, we have made the following changes to the manuscript, replacing the original wording in the Methods section on page 6 with these sentences: “To limit the sample to those with at least moderate levels of depressive symptoms and sleep data, but excluding those with a pattern of severe mental illness that has progressed into a distinct psychotic or recurrent mood disorder, the following criteria were applied...” We hope this change clarifies our intended meaning.

R2.2. Methods, Sample, Inclusion criteria b, page 6. Sleep onset between 8 p.m. and 6a.m. indicated not having "highly disrupted patterns of sleep onset" in individuals aged 12 to 25 years. I do not agree with this definition. Could you please back up your claim by giving references (other than #7 or #10-#12) here. Please reconsider, and this may mean that you need to calculate new analyses.

As this study only focused on a comparison of ‘normal’ sleep onset with ‘delayed’ sleep onset in depressed young people, participants (n = 8) who reported a habitual bed time in daylight hours (e.g. between the hours of 07.00 and 19.59) were excluded as they represented a sleep phenotype beyond the scope of this paper. We have modified the inclusion criteria to more appropriately reflect this and omitted the phrasing ‘highly disruptive’ as it may have included individuals who weren’t “disrupted” but e.g. engaged in some types of shift work. Instead, the following sentences have been added to the inclusion criteria on page 7: “Inclusion Criteria C: A self-reported habitual sleep onset within normal (08.00 – 01.59) or delayed hours (02.00 – 06.00). As this study focused only on a comparison of normal and delayed phenotypes, participants who reported habitual bedtimes in daylight hours (e.g. 07.00 – 19.59) were excluded (n = 8).”

To further address the reviewer’s concerns, we repeated the statistical analysis with more conservative and restricted hours for the normal (21.00 – 01.59) and delayed (1.59 – 05.00) sleep phenotypes. In this
analysis, the prevalence of delayed sleep remained at 18%. There were no changes in significance and the final multivariate model also reflected the original findings. As such, the original cut-offs determined by previous literature (Clarke & Harvey, 2012; Lack, 1986) were retained. This also allows the current study to be compared with others using International Classification of Sleep Disorders (ICSD) definition (American Academy of Sleep Medicine, 2001). The following sentence was added into the manuscript, under the section ‘Analysis’ on page 11: “A final sensitivity analysis for a more restricted exposure, repeated the above approach but categorised those with a sleep onset of 21.00 - 01.59 as “normal” and those from 02.00- 05.00 as “delayed” onset.” The results of this sensitivity analysis were then included in the Results section on page 13: “The sensitivity analysis using the more restricted exposure categories of ‘normal’ (21.00 - 01.59) and ‘delayed’ (02.00 - 05.00) showed no differences in results.”

R2.3. Methods, Sample, Exclusion criteria c, page 6. Readers may not know what is meant by "persistent reoccurrence - stage 3". Please explain here.

We apologise for the ambiguity of this phrasing. In the context of the current study, “persistent reoccurrence” refers to a mental illness that has become chronic and otherwise long lasting in its effects (McGorry et al., 2007). It is usually determined by the presence of symptoms for a significantly sustained period of time, in addition to a non-response to treatment (Hickie et al., 2013). It is accompanied by a poorer level of social and occupational functioning than subthreshold patterns of mental illness. To more appropriately convey this to the readers, we have made the following text changes to the Methods section, under the heading Sample on page 7: “The presence of a psychotic mental illness or recurrent mood disorder that has had incomplete remission and is associated with deteriorating social, educational, occupational functioning due to persistent or reoccurring symptoms. This is described as a Stage 3 mental illness as outlined in the Clinical Staging Model (Hickie et al., 2013).”

R2.4. Methods, Analysis. The exploratory nature of the study is not an excuse for not calculating the correction for multiple testing. There are many appropriate methods to calculate the adjusted P-values. Please calculate, so that the readers can judge the statistical (and clinical) significance of your results.

We apologise for not including an alpha value correction for the analyses in the original submission. We have calculated a Bonferonni correction for the univariate tests and included the revised critical alpha level ($p < .004$) in the Methods section under Analysis on page 10. Furthermore, we have added an extra column to Table 1 (pg. 21) to display the $p$ values found. In the revised manuscript, only those variables with $p < .004$ in the univariate analysis (Table 1) are reported as significant and discussed in the Results on page 12. We propose that without knowledge of potential confounding patterns, an empirical approach of including variables with a univariate association statistical significance of $p < 0.5$ in the multivariate analysis is supported. Some authors propose the use of even more conservative approaches of e.g. an a priori $p$ value $< 0.1$ for inclusion of a variable. For the logistic regression analysis, only 7 variables were included; thus no correction for multiple testing is needed. As such, Table 2 and reported results remain as is.

The following paragraph was added into the Methods section, under the heading ‘Analysis’ on page 10: “Due to the number of t-tests conducted for the continuous clinical measures ($n = 12$), a Bonferonni correction was made for the univariate analyses. The adjusted alpha level for statistical significance for
reporting such univariate associations was determined to be \( p < .004 \). However, the multivariate analysis conservatively included all variables with \( p < .05 \).

To further reflect the alpha level correction, we have altered the discussion to only discuss the univariate results that achieved significance at \( p < .004 \). Thus, the revised paragraph on page 14 now states: “In this sample, delayed sleepers did not have significantly different symptom profiles, and, importantly, no greater levels of depression symptom severity. This suggests that delayed sleep isn’t a marker for depression severity in a depressed sample but rather something qualitatively different about this group. Neither did they differ in age, self-reported functioning, employment and disability. Suggested differences in education and function did not withstand adjustment for multiple testing.”

We believe that these changes will assist readers in understanding both the statistical and clinical significance of the relationships explored in this paper.

**R2.5. Authors Contributions, page 18. It appears that one of the authors named on the title page has no author contribution. Please explain.**

We apologise for this oversight. Dr Elizabeth Scott was involved in the design and implementation of the study as well as the critical revision of the manuscript. The Author’s Contributions section on page 19 has been amended to reflect this:

“The study was designed and conducted by PM, NG, IH, RP, CP, PA, DH and ES. The analysis of data and interpretation was conducted by BOD and NG. The paper was prepared by NG, BOD and critically revised by PM, IH, CP, PA, DH, RP and ES.”

**R2.6. Methods, Sample, page 5. Please give more details, what are these headspace clinics. Who owns them? Are they private or public? What is their catchment area? Are patients admitted with a referral or also without a referral? I ask this, as on the basis of this information the readers can judge, whether the sample was a selected one and due to it to which extent the sample was biased. Please clarify.**

We apologise for not including this information in the original submission which would be confusing to others outside the Australian health system. The following paragraph has been added to the Methods section, under the heading ‘Sample’ on page 6: “Established by the Australian Government in 2006, Headspace centres provide youth-focused mental health and general health services, drug and alcohol services and vocational assistance to young people aged 12-25 years. There is direct access with no need for a clinician referral and no specific catchment area. There are currently 40 centres located nationally, the four in this study being amongst the first established. The most common reasons for attendance at Headspace are mental health problems, primarily anxiety and depressive symptoms, often in the context of psychosocial issues such as relationship conflict with family and peers (Rickwood, Telford, Parker, Tanti, & McGorry, 2014). As Headspace focuses on both youth mental health and early intervention, young people may present for care with varying illness severity (e.g. subthreshold symptoms - severe symptoms, mild – severely impaired functioning) across a range of mental health problems (Scott et al., 2012).” We have included the following papers describing this service in the revised manuscript:


**R2.7. Assessment, Sleep, page 7.** The paragraph starts with "Other ...". To which this "other" refers to? Why did not you just start with "Sleep characteristics ..."? Please clarify and correct as appropriate.

**Reply to R2.7.** We agree with this suggested change. The first paragraph of the Assessment section in the Methods has been amended on page 8 and now states “Sleep characteristics were assessed using...” In the original submission, “other” referred to all of the sleep characteristics (i.e. time spent in bed, time taken to fall asleep, sleep duration, sleep quality and fatigue) except wake time and sleep time as these were presented in the inclusion/exclusion criteria section of the method. We apologise for this ambiguity.

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**R2.8. Assessment, Demographics and psychosocial risks, page 8.** There were individuals not participating in any type of educational study. Were there such individuals among those aged 12 to 15 (or 16) years? If yes, please explain how it is possible. I ask this, because certainly there is the school age in Australia, or is not there?

**Reply to R2.8.** Although in Australia it is compulsory to attend school until the age of 16, some of the current participants are vulnerable to long periods of school absences due to mental illness and its associated lapses with social and occupational functioning. Therefore, at the time of the study 7 school age participants were not attending school regularly, although they were likely enrolled in some form of educational establishment.

We hope these changes to the original manuscript are in accordance with the reviewers’ suggestions, and we look forward to further correspondence with you.

Kind regards,

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References


