

Format for ANSWERING REVIEWERS

May 30, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 10687-revised.doc).

Title: Association between Resting Energy Expenditure, Psychopathology and HPA-Axis in Eating Disorders

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers:

(1) Reviewed by 02445261

1) *The manuscript is interesting and well-written; i believe that the most important limitation of this study is the small sample size that did not allow the generalization of the main findings*

Re: The mentioned limitation was added in the text, as suggested (page 11).

2) *Results section within the same section should be reduced in length as too long as presented .*
The results section was shortened, as requested (page 2).

3) *Throughout the Introduction section, the authors could provide more details about the main mechanisms of action underlying the increased hypothalamus adrenal axis (HPA) arousal in the sample of 43 subjects with eating disorders. What is the main HPA dysfunctions (hyperactivity/ lower post-dexamethasone cortisol plasma levels/elevated levels of androgen precursors) in subjects with eating disorders? Could life stressors and hormonal dysregulation in the HPA axis be considered as common factors playing a role in eating disorders ?*

Re: the introduction was integrated, as suggested (page 4).

4) *Throughout the Methods section, the main socio-demographic characteristics of participants could be better summarized in a specific Table .*

Re: socio-demographic characteristics was added (table 1, page 17).

5) *Also, the authors stated that the exclusion criteria were comorbid schizophrenia or bipolar disorder, illiteracy, mental retardation, severe medical conditions, and current use of psychoactive medications. Did the authors consider as inclusion criteria comorbid anxiety (Axis-I) or personality (Axis-II) disorders? If so, this should be specified*

Re: Personality disorders were not assessed. The present limitation was added in the text (page 11)
Anxiety disorders did not represent a specific exclusion criterion.

6) *The authors reported that 43 female participants (22 with AN restricting type, and 21 with BN binge/purging type) have been recruited as the final sample. Did they use the structured clinical interview for DSM-IV axis to confirm psychiatric diagnoses ?*

Re: The mentioned information was provided, as requested (page 5).

7) *Figure 1 is difficult to distinguish for the general readership and should be improved regarding resolution.*

Re: Power Point versions of Figure 1 and Figure 2 were provided for a better resolution.

(2) Reviewed by 00742104

1) *Although the paper is very well written there are some points that need to be revised. Firstly, the status of the patients have not been explained in sufficient detail. Was this a first time diagnosis? Were the patients in remission? Since when had they been diagnosed with an ED?*

Re: The mentioned information were provided, as requested (page 5).

2) *Patients were included in the study if they reported at least 1 year of a stable Eating Disorder diagnosis , were none of the 43 patients included using psychoactive medications (which was an exclusion criteria) and if not why not ?*

Re: We excluded pharmacological treatments which can interfere with HPA Axis response (i.e.: Antidepressants use could increase human hippocampal neurogenesis by activating the glucocorticoid receptor: Anacker and Pariante et al., 2011). According with the Reviewer's observation, this specification was added in the text (page 5).

3) *The authors argue that there is a relationship between severe AN and a higher REE due to the association between shape concern and cortisol, but what the study failed to show was an association between weight concern and cortisol and the total EDE-Q score. No explanation is given as to why they believe an association with shape but not weight concern occurs.*

Re: considering the small sample size, some of the interactions (including the effect of EDE-Q weight concern) could result significant in further studies. This specification was added in the discussion (page 11). However, it is of note that, as reported in the text, several authors pointed out that body image concerns and distortion represent the core psychopathological feature of eating disorders patients.

4) *Studies have shown that in underweight anorexics, the pituitary responds to corticotropin-releasing hormone, being restrained in its response by the elevated levels of cortisol . I believe it is difficult to explain this increase due psychological causes rather than metabolic.*

Re: Given the cross-sectional design of the study, we are not able to derive final conclusion on causal relationship psychopathology and REE. The present mediation model support a strong mediator role of cortisol, suggesting a possible underlying mechanism. However, it does not explain all the variance of the mentioned association, which could be caused by other metabolic factors related to underweight in AN patients. The present point was discussed in the text, according with the Reviewer's observation (page 10,11).

(3) Reviewed by 00058344

1) *The authors need to make clear (1) that the adaption for 45 min is enough to measure "REE"*

We agree with the reviewer comment and the method section was improved with a better description of the methodology adopted to measure REE (page 6).

2) *whether the patients are in the recovery phase. The data in the admitted patients are valuable to evaluate the real "REE" in AN patients .*

Re: None of the patients were in a remission or recovery phase of disease. This specification was added in the text (page 5).

(4) Reviewed by 00000663

(1) If I understand their assumption, shape concern might increase cortisol, which in turn would be responsible for higher REE. 1. This assumption is supported by statistics, but I wonder whether shape concern is the correct value to start from; I would have preferred to see an analysis of total EDE values, which unfortunately were not associated with REE. The authors should explain why they believe that the focus should be given to shape concern, not to e.g. weight concern, which similarly differed between anorexia and bulimia. 2.

Re: the model was tested with all the available psychopathological measures, and EDE-Q shape concern provided the best fit for the tested model. According with the Reviewer's observation, this point was better explained in the text (page 9, lines). Considering the small sample size, some of the interactions (including the effect of EDE-Q weight concern) could result significant in further studies. This specification was added in the discussion (page 11). However, it is of note that, as reported in the text, several authors pointed out that body image concerns and distortion represent the core psychopathological feature of eating disorders patients (page 11).

(2) The activation of HPA axis and increased REE might also stem from more severe metabolic abnormalities present in anorexia, not specifically due to psychopathology. According to this hypothesis, HPA axis and shape concern would not be linked by a causal relationship.

Re: Given the cross-sectional design of the study, we are not able to suggest final conclusion on causal relationship between the variables. Mediation models are useful strategies to propose possible mechanisms underlying specific associations between variables. Cortisol levels appear to be a full mediator of the association between psychopathology and REE. However, it does not explain all the variance of the mentioned association, which could be caused by other metabolic factors. This specification was added in the text, according with the Reviewer's comment (page 10,11).

(3) In Table 2, the association between SCL-90 and EDE-Q in anorexia would be marked as significant.

Re: Table 2 was corrected, as suggested. We apologize for the mistake (Table 2, page 18).

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*.

Sincerely yours,

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