Author’s response to reviews

Title: Novel causes and consequences of overtraining syndrome: the EROS-DISRUPTORS study

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Author’s response to reviews:

Technical Comments:

Editor Comments:

In consultation with one expert Section Editor, we have decided to proceed once the following changes have been addressed.

R. We fully addressed the suggested changes. Besides, we provided a detailed explanation regarding the proposed 13.7:1.0 ratio as a cutoff for testosterone-to-estradiol ratio.

All points raised were highly consistent and helped raised the quality of the paper even with slight changes, and showed that the review was performed very thoroughly in a quite constructive way.

Section Editor

Lines 31-2

Mentioning the title of a previous article that way in the Abstract is a bit awkward. Would that be better off referenced in another way at that point (“In a previous study, we showed . . .)?

R. We fully agree. In addition, other changes regarding the name of the study were performed:

“…remain unclear. Although multiple markers of OTS have recently been identified, the independent influence of OTS on hormones and metabolism have not been assessed. Hence, the objective…”
“…independently modifies the behaviors of clinical and biochemical parameters, using novel data from the EROS study.”

“we performed two clusters of statistical analyses using the full data of the Endocrine and Metabolic Responses on Overtraining Syndrome (EROS) study, in a total of 117 markers.”

“Conclusions: The EROS-DISRUPTOR study unveiled that OTS can be independently triggered by eating patterns, regardless of training patterns, while…”

Line 38

“ATL” is used as an abbreviation without having been defined.

R. “(OTS-affected athletes (OTS) = 14 and healthy athletes (ATL) = 25)…”

Line 80

Start a new sentence beginning with “Although” because this one is too long.

R. We corrected accordingly.

Lines 93-6

Combine this with previous paragraph and remove “Hence” from the beginning of the paragraph that follows because it is a new paragraph.

R. We corrected accordingly.

Lines 107-16

In-text lists should be numbered to improve readability:

“For the present analysis, we performed a comprehensive joint statistical analysis of data from five of the arms of the EROS study, including four of primary findings: 1.) the EROS109 HPA axis in which we evaluated the hypothalamic-pituitary-adrenal axis hormonal responses in athletes (4); 2.) the EROS-STRESS, . . .”
I believe the citation range that is being referred here is 10-14, not 4-8. The authors should make sure all of the citation numbers in their revised version are correct with the additions that they have made.

R. We apologize for this mistake. We performed a thorough review and corrected the references.

Line 114
Colon after “hormones” maybe?
R. “4.) the EROS-BASAL, in which we evaluated: basal hormones; inflammatory; immune; and muscular parameters”

Line 129
Change “specific” to “specified” or another appropriate word that is a verb.
R. That was perhaps a typing mistake. We corrected accordingly.

Line 136
Change “moderate-to-intensity” to “moderate-to-intense”
R. We corrected accordingly.

Line 160
Insert “the fact that” between “Despite” and “additional”

+ 

Line 161
Explain “not eligible”
R. We heavily changes this sentence to improve readability:
“Additional analyses of the excluded parameters n were also performed, but were not included”
Line 162
Decimal places in a sentence should be consistent; in this case: “3.5% and 3.0%”
R. We corrected accordingly.

Line 195
NCS group? What group was that? Not defined.
R. This was the group of sedentary control, but was not included for the present analysis (since the identification of predictors of OTS needs to based on levels expected for athletes, not in general population).
Thus. we removed: “and 12 for the NCS group”

Line 204
Change “has” to “had”
R. We corrected accordingly.

Line 230
Might it be more insightful to also state this as a percentage change?
R. That was the percentage change, we forgot to insert the symbol.

Line 236
Remove “show to”
R. We corrected accordingly.

Line 263
Missing close of parentheses.
R. We corrected accordingly.

Lines 267-70

Can this important statement be divided into two sentences to improve readability?

R. We divided this sentence, which did improve readability:

“Our aim was to identify whether and how the mere presence of OTS modified the behaviors of the tested parameters. Specifically, among the intrinsic mechanisms of OTS, which were inherently responsible for at least some of the dysfunctional changes found in OTS, as consequences, not causes, of OTS.”

Line 322

Might it be better to simply write out “odds ratio” as you do everywhere else you use it (in other words, remove its abbreviation in places where you use the abbreviation along with the term and then just write it out here)?

R. We removed the abbreviation and replaced for “odds ratio”. It makes much more sense.

Line 331

Insert “the influence of” between “as” and “each of them”

R. We inserted accordingly. Changes like this have great positive influence on the quality of the sentence. Thanks!

Line 336

Present tense so “help”

R. We corrected accordingly.

Line 368
Be consistent with decimal places in sentence (see above) and, far from my areas of expertise, but isn’t a test failure in drug-tested sports > 6:1? Is this a different way to state the ratio because if not, you are suggesting a ratio that will get you suspended?

R. The testosterone-to-estradiol ratio is a recent proposal as an indirect evaluation of the level of aromatase activity, as almost all estradiol in males comes from the conversion from testosterone.

Increase in estradiol levels may come either physiologically- or pathologically. In the first case, estradiol increase occurs as a consequence from an increase of testosterone levels (due to either increased LH (and at a lower extent, FSH) stimulation, or exogenously. In this case, aromatase activity is neither exacerbated nor blunted, so estradiol increases proportionally to testosterone, which preserves the ratio between them.

Several studies in the past years observed beneficial effects of increased estradiol on males, on sexual function, muscle mass, bone density and quality, and energy levels, but only when accompanied by increased testosterone. On the other hand, too much suppression of aromatase activity (e.g., anastrozole use) blunts some of the benefits of increased testosterone, as the T:E ratio becomes too high.

Conversely, in the second case, estradiol increase occurs as a consequence of pathologically exacerbation of aromatase activity, not due to testosterone increase. Hence, an estradiol increase results in decreased testosterone, which was overwhelmingly used for the conversion into estradiol, leading to reduced T:E ratio. Many studies have observed that a decreased ratio is present in metabolic and inflammatory diseases, such as obesity and diabetes, for example.

A joint analysis of testosterone and estradiol levels and its proportion is better visualized in a single ratio, the T:E levels.

The ratio of > 13.7:1.0 was found by us but was also proposed at very similar levels by other groups, that found this cutoff from independent findings from us, which increases its strength. However, this is when total testosterone is expressed in ng/dL and estradiol in pg/mL.

We have now highlighted this point in the text, and adjusted the decimal places.

“The EROS study showed that a T:E ratio should be greater than 13.7:1.0 (for total testosterone and estradiol are expressed in ng/mL and pg/dL, respectively)”

Line 393

Change “overtraining” to “excessive training” because you are referring to it as OTS even if that is (as indicated by your findings) a misnomer.
R. You are absolutely right. We were causing a “misleading interchangeable expressions” of OTS and “excessive training” as being similar. We corrected accordingly.

Lines 419-421

I do not understand this sentence. In both cases, you are referring to athletes who perform those things exclusively. Shouldn’t it be “collectively” in the first case? Please clarify because it does not make sense as written.

R. The sentence was a bit confusing indeed. We changed for clarification, as below:

“The EROS study only evaluated male athletes that practiced either both endurance and strength modalities, or sports that demand both endurance and strength efforts. As the present study did not analyze athletes of endurance, strength, or explosive (“stop-and-go” sports, such as ball games) modalities, it is uncertain whether the findings on OTS can be replicated to these athletes, as well as female athletes.”

Line 436

Change “Worse” to “worsened” to describe body composition for tense consistency with adjective that describes mood.

R. We changed accordingly.