

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Clinical Pediatrics*

**Manuscript NO:** 86964

**Title:** Brain metabolic profile assessed by magnetic resonance spectroscopy in children with down syndrome: Relation to intelligence quotient

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 07509868

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** Egypt

**Manuscript submission date:** 2023-07-17

**Reviewer chosen by:** Geng-Long Liu

**Reviewer accepted review:** 2023-08-24 05:01

**Reviewer performed review:** 2023-08-26 01:42

**Review time:** 1 Day and 20 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

<b>Scientific significance of the conclusion in this manuscript</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

## SPECIFIC COMMENTS TO AUTHORS

This is a very interesting study, but much additional work needs to be done regarding methodology, results, and Discussion.

- Multiple t tests, No Bonferroni correction, is a big problem that affects the interpretation of the results of this study. Whenever multiple statistical tests are made simultaneously, chance error creeps in and yields some significant results that are spurious. To control for this problem, Bonferroni developed a procedure that helps identify spurious findings. Alternatively, this problem can be addressed by selecting a more conservative alpha level. For this study, using  $p < .01$  instead of  $p < .05$  would help ameliorate the problem. By applying either the Bonferroni formula or choosing  $p < .01$ , the results (and therefore the interpretation of the data are changed as follows: (a) In Table 2, the Naa/Cr correlation in the Frontal lobe is significant, and neither the Naa/Cr nor the Cho/Cr correlation in the Occipital lobe are significant; and (b) In Table 3, only one of the correlations with IQ remains significant (F Naa/Cr).
- Why unpaired t tests? Groups were matched on age, and to some degree, on sex. Matched samples require paired t tests, not unpaired. And why multiple t tests instead of multivariate analysis?
- Why were 20 of the original 60 DS



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children eliminated from study? What is the rationale? Of the 20 eliminated, how many couldn't perform the required tasks and how many were simply removed from the sample for unnamed or unknown reasons? 4. "The IQ was primarily influenced by . . ." Implies causality. One cannot infer causality from correlations, just relationships. 5. There is no way to interpret the results as having anything to do with DS. The authors compared MRS data for one group with average IQ and one group with low IQ. The results may apply to low functioning children in general, but no differences can be attributed to the DS diagnosis. This serious limitation points to another methodological problem with the study—the authors should have included a third group, namely low functioning children and adolescents who do NOT have DS. 6. The authors computed 3 ratios in 4 regions of the brain, for a total of 12 comparisons. They provided excellent scientific rationales for their selection of the specific ratios and brain regions to explore. But they did not hypothesize which of these 12 were most likely to be significant based on scientific rationale and previous research results; from multiple MRI studies on individuals with DS. Instead, they used a "shotgun" approach to find out what was significant and what was not. Whenever that type of approach is used, significant findings need to be cross-validated with a new sample before they can be meaningfully interpreted. Despite the fact that the authors did not rely on the relevant MRI literature to formulate specific hypotheses, they did an excellent job in the Discussion section of integrating their findings with previous results.

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

### SPECIFIC COMMENTS TO AUTHORS

The revision addressed some of my concerns adequately. I appreciate that the authors conducted a multivariate analysis and added some of my concerns as limitations of their study and as suggestions for future research. However, the one comment that I do not agree with concerns multiple comparisons. The argument that “only two samples are compared” is not important. Table 2 makes 12 simultaneous comparisons. So does Table 3. Following the strict Bonferroni procedure, using  $p < .004$  will yield a family-wise alpha level of .05 (the Bonferroni formula is .05 divided by the number of simultaneous comparisons, in this case 12, which yields  $p < .004$ ). However, since this procedure is conservative, a more liberal level would be  $p < .01$ . That would be acceptable for this study. But using  $p < .05$  is not acceptable.