

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Clinical Characteristics and Outcomes of Hyponatraemia Associated with Oral Water Intake in Adults: A Systematic Review
<b>AUTHORS</b>	Rangan, Gopala; Dorani, Nilofar; Zhang, Miranda; Abu-Zarour, Lara; Lau, Ho Ching; Munt, Alexandra; Chandra, Ashley; Saravanabavan, Sayan; Rangan, Anna; Zhang, Jennifer; Howell, Martin; Wong, Annette

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Topliss, Duncan Alfred Health, Endocrinology & Diabetes
<b>REVIEW RETURNED</b>	26-Feb-2021

<b>GENERAL COMMENTS</b>	<p>This is a comprehensive review of this specific topic of dilutional hyponatraemia associated with oral water ingestion.</p> <ol style="list-style-type: none"><li>1. The main concern is that most of the data is derived from individual case reports and in all reviewed publications water intake is only an estimate so that the accuracy of identification of the quantitative risk intake is low.</li><li>2. The identified associated symptoms of dilutional hyponatraemia are well-known already and this should be acknowledged.</li><li>3. Exercise-associated hyponatraemia eg in long -distance running, especially in hot weather, appears to be linked to replacement of sweat loss (water plus electrolytes including sodium) with oral water intake. This could be made more explicit in the discussion.</li><li>4. Can any statement be made about the relative merits of hypertonic versus isotonic fluid administration in oral water intoxication? In general in SIADH use of isotonic fluid administration may worsen the hyponatraemia as the sodium is excreted in concentrated urine with retention of the administered water compounding the hyponatraemia. Is this an issue in these patients? Isotonic saline is most helpful in hyponatraemia associated with hypovolaemia.</li><li>5. Do these data support the increased risk of osmotic demyelination with rapid correction in chronic versus acute hyponatraemia?</li></ol>
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<b>REVIEWER</b>	Ito, Hiroshi University of Tsukuba, Division of Hospital Medicine
<b>REVIEW RETURNED</b>	09-Mar-2021

**GENERAL COMMENTS**

The authors described the clinical characteristics of the cases of hyponatremia due to water intoxication. I read this manuscript with interest because the underlying causes of water intoxication were not limited to psychogenic situations. Patients with urinary tract infections who were advised to drink water were also at risk of developing hyponatremia. At this point, this manuscript seems of educational value. However, there are several concerns about this manuscript as follows.

Page 2.

- Please unify the notation of IQR in the Results. The authors described the IQR of the water intake as "IQR 6 to 13L/day." However, according to other notations in this section, this should be "IQR: 6-13."
- Generally, the p-value reflects both the difference in central tendency and the number of observations, which would make the interpretation of the results complicated. Thus, the authors should present odds ratios and 95% confidential intervals instead of the p-value.

Page 8.

- The authors described the main conditions of patients being schizophrenia (45%), psychogenic polydipsia alone (16%), depression (2%), and other (19%). Does this mean the remaining 18% of patients were previously healthy?
- According to the authors, there was heterogeneity in the method of reporting the volume of water. Please provide examples of measuring the volume of water. For instance, we can estimate the amount of water by body weight change. Another method includes self-report from the patients.

Page 9.

- As mentioned above, the p-value reflects the difference in central tendency and the number of observations. From this perspective, the authors should use expressions other than p-value (e.g., median, odds ratio, 95% confidential intervals).

Page 10.

- The authors described several primary associated factors of excessive water intake. Were there any differences in the severity of hyponatremia according to these factors?

Page 12.

- The authors described the treatment types being water/fluid restriction (15%), hypertonic saline (11%), isotonic saline (9%), antipsychotic medications (7%), diuretics (4%), behavioral therapy (2%), and the other (15%). Does this mean the remaining 37% of patients received no treatment?
- The sodium overcorrection is a typical complication in treating water intoxication, especially in patients receiving isotonic saline. Were there any differences in the risk of this complication among the treatment types?
- The authors used the expression "the rapid overcorrection of hyponatremia," but this is not concrete. Please describe the rate of the correction in this situation.

Figures

	<ul style="list-style-type: none"> <li>• Figure 2B, 2D, 3D, 4A, and 4B should be presented as Venn diagrams to make them easy to understand.</li> </ul>
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<b>REVIEWER</b>	Hew-Butler, Tamara Wayne State University, Exercise and Sport Science
<b>REVIEW RETURNED</b>	20-Mar-2021

<b>GENERAL COMMENTS</b>	<p>This Systematic Review of either 177 studies (or 199 Case Reports?) by Dorani N et al confirms four main conclusions with regards to the development of hyponatremia from primarily oral water intake: 1) individuals who develop hyponatremia drink ~8L/24-hours on average; 2) cognitive deficits, seizures and vomiting are the main symptoms of water intoxication; 3) females are more at risk for severe hyponatremia; and 4) water restriction is the main treatment for hyponatremia due to oral water intoxication. These collective conclusions are not surprising (nor new) given our understanding of hyponatremia from the first documented case fatality reported in 1935 (ironically, in a 50-year-old female given 9L of tap water by proctoclysis over 30-hours post-surgery). The authors should be commended for their extensive literature search and rigorous data collection (mostly reported as Supplemental information). However, a more critical pathophysiological interpretation of these reports is required to significantly enhance our overall knowledge of the many nuances which would progress our understanding of this highly complex (and life-threatening) clinical entity. I offer the following suggestions for improvement:</p> <p>Title and text: The spelling of hyponatremia/hyponatraemia should be consistent throughout the title and the text. It is not appropriate to switch between American English and British English spellings within one manuscript.</p> <p>Abstract: Under Results, it is confusing that 177 article were included for review, but there were 199 case reports. Please clarify (199 individual cases and 24 case clusters within 177 different papers?)</p> <p>Page 3, line 19 – Heterogenity, I believe, should be heterogeneity.</p> <p>Page 3, line 56 – hyponatremia is misspelled (hyponatrameia)</p> <p>Methods section is unduly long and still confusing, especially compared to the results and discussion</p> <p>Page 5, lines 22 and 24-25 – no need to capitalize common nouns (Review, Syndrome of Inappropriate Antidiuretic Hormone Secretion)</p> <p>Page 5, lines 47 – I still don't understand what is a "relevant" or "Irrelevant" article</p> <p>Page 6, Risk of bias paragraph – please define what "bias" represents and why the need to develop your own scale?</p> <p>Page 6, Data synthesis paragraph – please explain more clearly what you are comparing and why the need to perform chi-squared and ANOVA tests (since most of your data is from individual case reports).</p>
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Page 7, Results section paragraph – the mathematics of your studies still required clarification: the authors included 177 articles, of which 199 were case reports and 24 were case series?? Where these included in the 177 or in addition to that total? This is not explained well.

Page 7, Risk of bias assessment – I still have no idea what constitutes “bias”; thus Table 1 has no meaning in the current context. The authors often refer to supplementary data and files which are too numerous for the reader to sift through for clarity. The bulk of the data exists in these supplementary files, but their collective significance remains highly confusing in the larger context as currently explained. Why is bias this important in the results and interpretation of these data??

Page 9, line 22 – Do not begin a sentence with a number (Twenty-four percent...)

Page 10 (?) or page 12 of 112)?? – in paragraphs starting with “The primary factors of excessive water intake...” How is polydipsia a factor associated with water intake? Polydipsia is defined by excess water intake. Also how can water intake be iatrogenic? Did physicians offer the wrong advice which caused hyponatremia?? Please clarify these terms (or at least define them in context).

Page “1” (pagination was lost after page 9) under “outcomes” – please explain or define “unresolved”. Does that mean serum [Na+] did not change from the baseline value??

The discussion section is under-developed, especially with regards to explaining the significant pathophysiology underscoring your results in the context of the VAST AMOUNT OF LITERATURE AVAILABLE ON THIS TOPIC. Do not just spit out your results and support them with other review papers. What do YOUR results add to our understating and drive changes in clinical care?

Page “1” first paragraph if the Discussion section – if you start the abstract and Introduction with four aims in numerals (1; 2; 3; 4), do not switch back and forth to letters (i; ii; iii; iv)

Page “1” 4th paragraph in the discussion, line 42 – in the 11% of patients with no resolution, does “resolution” refer to biochemical or clinical resolution?

Page “1” of next page, line 3 – patients with diabetes insipidus rarely develop hyponatremia – please explain the context of this explanation.

Page “1” under the section explaining rhabdomyolysis as a complication – why would rehydration be an appropriate treatment during a concomitant state of water intoxication – please consider the pathophysiology more completely as this is a complex problem.

There are only 44 references, many of them review papers on the topic in the main body of this systematic review. A systematic review should be a well-developed and well-referenced synthesis of the literature on the topic. Readers should not have to toggle between supplementary data and the main body of the text to gain

	<p>context of what these data contribute to OUR OVERALL UNDERSTANDING of the important nuances of these findings. FOR EXAMPLE, the first main finding that the median oral water intake for developing hyponatremia is 8L/day is exceedingly misleading.</p> <p>The data are heavily skewed (Figure 3a) to the left and this important finding is not addressed in the discussion section. What is the average free water excretion rate of the kidneys (700-1200ml/hour)?</p> <p>What is the impact of free water renal excretion rates on the development of hyponatremia?</p> <p>What about the likely confounding variables that induce SIADH and the development of hyponatremia??</p> <p>Since most of your cohort studies involved clear non-osmotic stimuli to AVP secretion (anti-psychotic medications, stress, exercise, etc.) this section warrants an extensive revision. In fact, all four of your main conclusions require critical reflection with regards to the vast pathophysiological significance of your findings to more comprehensively enhance our broader understanding of this topic.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewer 1

Comment #1: The main concern is that most of the data is derived from individual case reports and in all reviewed publications water intake is only an estimate so that the accuracy of identification of the quantitative risk intake is low.

Author Response: We agree with Reviewer #1 that this is the main limitations of the study. To address this concern, the limitation has been added to the Abstract (page 2) and the limitations section in the Discussion has been re-worded and updated on page 19-20.

Comment #2: The identified associated symptoms of dilutional hyponatraemia are well-known already and this should be acknowledged.

Response: We agree with Reviewer #1 and this comment has been acknowledged in the Discussion on page 18 (paragraph 3) and reference has been added to support this statement.

Comment #3: Exercise-associated hyponatraemia eg in long -distance running, especially in hot weather, appears to be linked to replacement of sweat loss (water plus electrolytes including sodium) with oral water intake. This could be made more explicit in the discussion.

Response: Thank you for the comment. We have added details of exercise-associated hyponatraemia to the Discussion on page 16 and added appropriate references.

Comment #4: Can any statement be made about the relative merits of hypertonic versus isotonic fluid administration in oral water intoxication? In general in SIADH use of isotonic fluid administration may worsen the hyponatraemia as the sodium is excreted in concentrated urine with retention of the administered water compounding the hyponatraemia. Is this an issue in these patients? Isotonic saline is most helpful in hyponatraemia associated with hypovolaemia.

Response: Thank you for the comment. This is certainly an interesting point to discuss. Unfortunately, due to low quality of evidence in this systematic review and paucity of cases, it is not possible to make any recommendations based on our data. In addition, the published data and clinical practice guidelines also do not provide any distinction between the isotonic vs. hypotonic saline. To address this uncertainty however we have expanded the discussion of correction of hyponatraemia in the Discussion and added references that may be useful to readers to stimulate future studies (see pages 19-20).

Comment #5: Do these data support the increased risk of osmotic demyelination with rapid correction in chronic versus acute hyponatraemia?

Response: Thank you for the comment. As discussed in our response to Comment #4, above we have expanded the Discussion to address this uncertainty, and in particular emphasise the importance of taking a cautious approach when correcting sodium levels in chronic hyponatraemia, based on clinical practice guidelines.

Reviewer: 2

Comment #6: Page 2. Please unify the notation of IQR in the Results. The authors described the IQR of the water intake as "IQR 6 to 13L/day." However, according to other notations in this section, this should be "IQR: 6-13."

Response: Thank you for the comment. We have replaced the IQRs with 95% confidence intervals, as suggested in comment #7.

Comment #7: Generally, the p-value reflects both the difference in central tendency and the number of observations, which would make the interpretation of the results complicated. Thus, the authors should present odds ratios and 95% confidential intervals instead of the p-value.

Response: Thank you for the comment. We agree and have removed the P-values and replaced them with 95% confidence intervals. In addition, due to heterogeneity of the data, odds ratio and a meta-analysis were not performed.

Comment #8: Page 8. The authors described the main conditions of patients being schizophrenia (45%), psychogenic polydipsia alone (16%), depression (2%), and other (19%). Does this mean the remaining 18% of patients were previously healthy?

Response: Thank you for the comment. The data in the manuscript has been extensively revised to improve clarity. This data is now reported in Table 4 (55% psychogenic, 12% exercise; 13% iatrogenic; 7% habitual/dipsogenic; 11% other).

Comment #9: According to the authors, there was heterogeneity in the method of reporting the volume of water. Please provide examples of measuring the volume of water. For instance, we can estimate the amount of water by body weight change. Another method includes self-report from the patients.

Response: Thank you for the comment. We have added more detail to the section of 'volume of water consumed' in the Results section (page 12). In particular we have added qualitative terms that were mentioned in individual case studies. In addition, details for the method of reporting can also be found in Supplemental Table 4.

Comment #10: Page 9. As mentioned above, the p-value reflects the difference in central tendency and the number of observations. From this perspective, the authors should use expressions other than p-value (e.g., median, odds ratio, 95% confidential intervals).

Response: We agree with the Reviewer and have removed P values and replaced them with 95% confidence intervals, as recommended.

Comment #11: Page 10. The authors described several primary associated factors of excessive water intake. Were there any differences in the severity of hyponatremia according to these factors?

Response: Thank you for the comment. We have extensively revised the data presented in the Results and the mode of presentation. In particular we have focused on grouping data according to the severity of hyponatraemia in Tables 4 and 5 as well as re-formatted the Figures and included 3D scatterbox plots to discern patterns rather than attempt to define associations, given the low quality of evidence of case reports.

Comment #12: Page 12. The authors described the treatment types being water/fluid restriction (15%), hypertonic saline (11%), isotonic saline (9%), antipsychotic medications (7%), diuretics (4%), behavioral therapy (2%), and the other (15%). Does this mean the remaining 37% of patients received no treatment?

Response: Thank you for the comment. We have extensively revised the data to simplify the main findings of the data. In Table 5, we have categorised treatments according to four categories: not reported, supportive care (which is defined in the text of results section, and includes treatment of the underlying cause, such as psychotic drugs), isotonic saline and hypertonic saline (see page 13 of the results). We felt that these categorisations will be more clinically meaningful for clinicians.

Comment #13: The sodium overcorrection is a typical complication in treating water intoxication, especially in patients receiving isotonic saline. Were there any differences in the risk of this complication among the treatment types?

Response: Thank you for the comment. Due to the heterogeneity in the data, it was not possible to identify any specific differences. However, to address this point we have extensively updated the Discussion to raise this point for future studies (page 19-20)

Comment #14: The authors used the expression "the rapid overcorrection of hyponatremia," but this is not concrete. Please describe the rate of the correction in this situation.

Response: Thank you for the comment. Due to variations in reporting in individual case reports, it was not possible to describe the definition of rapid overcorrection. Therefore we have removed this term in the Results and have instead updated the Discussion extensively to discuss this point (pages 19-20).

Comment #15: Figures. Figure 2B, 2D, 3D, 4A, and 4B should be presented as Venn diagrams to make them easy to understand.

Response: Thank you for the comment. On review of the manuscript we felt that our figures could also be improved, and therefore have placed quantitative data in Tables 4 and 5, and then developed completely new figures that better illustrate the patterns in the data that would be of interest to clinicians.

Reviewer: 3

Comment #16: A more critical pathophysiological interpretation of these reports is required to significantly enhance our overall knowledge of the many nuances which would progress our understanding of this highly complex (and life-threatening) clinical entity.

Response: Thank you for raising this important point. We agree and have therefore have extensively revised and re-written all sections of the manuscript, including the Introduction, Methods, Results, Discussion and References. In particular, we have added reference to classical articles Rowntree (1923) and Barahal (1938) as well more discussion on the pathophysiology of water intoxication in both the Introduction and Discussion.

Comment #17: Title and text: The spelling of hyponatremia/hyponatraemia should be consistent throughout the title and the text. It is not appropriate to switch between American English and British English spellings within one manuscript.

Response: Thank you for the comment. Spelling has been

Comment #18: Abstract: Under Results, it is confusing that 177 article were included for review, but there were 199 case reports. Please clarify (199 individual cases and 24 case clusters within 177 different papers?)

Response: Thank you for the comment. One hundred and seventy seven articles were included, but some contained multiple case reports, and is the reason why there were 199 individual cases and 24 case clusters. This has been clarified on page 9 of the Results and also a new Table 2 has been included to describe the characteristics of the individual studies (page 9-10)

Comment #19a: Page 3, line 19 – Heterogenity, I believe, should be heterogeneity.

Response: Thank you for the comment. This has been corrected.

Comment #19b: Page 3, line 56 – hyponatremia is misspelled (hyponatrameia)

Response: Thank you for the comment. This has been corrected.

Methods section is unduly long and still confusing, especially compared to the results and discussion

Response: Thank you for the comment. We have updated the Methods section to provide more clarity.

Comment #19c: Page 5, lines 22 and 24-25 – no need to capitalize common nouns (Review, Syndrome of Inappropriate Antidiuretic Hormone Secretion)

Response: Thank you for the comment. We have revised this section.

Comment #20: Page 5, lines 47 – I still don't understand what is a "relevant" or "Irrelevant" article

Response: Thank you for the comment. We have added a PICO table (table 1) to clarify the inclusion criteria for the study.

Comment #21: Page 6, Risk of bias paragraph – please define what "bias" represents and why the need to develop your own scale?

Response: Thank you for the comment. We have replaced the term "bias" with an assessment of quality of the studies. The scale was based entirely on an established method, the Newcastle-Ottawa Scale (NOS), designed for the assessment cohort studies/case-reports.

Comment #22: Page 6, Data synthesis paragraph – please explain more clearly what you are comparing and why the need to perform chi-squared and ANOVA tests (since most of your data is from individual case reports).

Response: Thank you for the comment. On re-considering the data in this paper, we also agree, and have removed the P values and ANOVA tests, and inserted 95% confidence intervals.

Comment #23: Page 7, Results section paragraph – the mathematics of your studies still required clarification: the authors included 177 articles, of which 199 were case reports and 24 were case series?? Where these included in the 177 or in addition to that total? This is not explained well.

Response: Thank you again for the comment. We hope that our modification as mentioned in response to Comment #20 address this point.

Comment #24: Page 7, Risk of bias assessment – I still have no idea what constitutes "bias"; thus Table 1 has no meaning in the current context. The authors often refer to supplementary data and files which are too numerous for the reader to sift through for clarity. The bulk of the data exists in these supplementary files, but their collective significance remains highly confusing in the larger context as currently explained. Why is bias this important in the results and interpretation of these data??

Response: Thank you for the comment. Please see our response to #Comment 21. In addition, we have updated the Results section to add more detail and summarised data in new Figures. The supplemental files are provided as tabulations of the raw data for interested readers only.

Comment #24b: Page 9, line 22 – Do not begin a sentence with a number (Twenty-four percent...)

Response: We agree, and this has been corrected.

Comment #25: Page 10 (?) or page 12 of 112)?? – in paragraphs starting with “The primary factors of excessive water intake...” How is polydipsia a factor associated with water intake? Polydipsia is defined by excess water intake. Also how can water intake be iatrogenic? Did physicians offer the wrong advice which caused hyponatremia?? Please clarify these terms (or at least define them in context).

Response: Thank you for the comment. We have updated the Introduction (page 4) and also revised the Methods section (page 7) to clarify these terms. Iatrogenic was defined as water intake that was undertaken by an individual based on medical advice, and we were also surprised by the number of cases that were identified that in the revised manuscript, explain this in more detail in the Discussion section (page 17).

Comment #26: Page “1” (pagination was lost after page 9) under “outcomes” – please explain or define “unresolved”. Does that mean serum [Na<sup>+</sup>] did not change from the baseline value??

Response: Thank you for the comment. For clarity, we have simplified the ‘outcomes’ into three categories: not reported, recovered (partial/complete) or death (see Table 5). The duration of the follow-up in cases varied but in the vast majority of cases, patients recovered from water intoxication.

Comment #27: The discussion section is under-developed, especially with regards to explaining the significant pathophysiology underscoring your results in the context of the VAST AMOUNT OF LITERATURE AVAILABLE ON THIS TOPIC. Do not just spit out your results and support them with other review papers. What do YOUR results add to our understating and drive changes in clinical care?

Response: Thank you for the comment. The discussion has been extensively revised and now includes additional relevant references.

Comment #27b: Page “1” first paragraph if the Discussion section – if you start the abstract and Introduction with four aims in numerals (1; 2; 3; 4), do not switch back and forth to letters (i; ii; iii; iv)

Response: Thank you for the comment, this has been corrected.

Comment #28: Page “1” 4th paragraph in the discussion, line 42 – in the 11% of patients with no resolution, does “resolution” refer to biochemical or clinical resolution?

Response: Thank you for the comment. This refers to biochemical hyponatraemia, and this has been updated in the revised manuscript in the Results and Discussion. The comment has been removed from the Abstract.

Comment #29: Page “1” of next page, line 3 – patients with diabetes insipidus rarely develop hyponatremia – please explain the context of this explanation.

Response: The Introduction has been extensively revised and updated.

Comment #30: Page “1” under the section explaining rhabdomyolysis as a complication – why would rehydration be an appropriate treatment during a concomitant state of water intoxication – please consider the pathophysiology more completely as this is a complex problem.

Response: This section has been extensively re-worded updated in the revised manuscript.

Comment #31: There are only 44 references, many of them review papers on the topic in the main body of this systematic review. A systematic review should be a well-developed and well-referenced synthesis of the literature on the topic. Readers should not have to toggle between supplementary data and the main body of the text to gain context of what these data contribute to OUR OVERALL UNDERSTANDING of the important nuances of these findings.

Response: Thank you for the comment. We have re-located the supplemental references (from Supplemental Data #1) to the main manuscript. Consequently, the references include all articles included in the systematic. In addition, a number of additional references have been added to improve the quality of the Introduction and Discussion. In addition, as mentioned the entire manuscript has been extensively revised to ensure that the manuscript provides a high-level contribution to the literature.

Comment #32: the first main finding that the median oral water intake for developing hyponatremia is 8L/day is exceedingly misleading. The data are heavily skewed (Figure 3a) to the left and this important finding is not addressed in the discussion section.

Response: Thank you for the comment. The discussion on the median oral water intake has been updated in the Discussion and in addition, new figures provide demonstrating individual data points provides more clarity on the data skewness.

Comment #33: What is the average free water excretion rate of the kidneys (700-1200ml/hour)?

Response: Thank you, we agree that this is an important point. Reference #6 has been added to the Introduction and Discussion, and this study demonstrates that the free water excretion rate of the kidneys is 735 to 970 mls per hour.

Comment #34: What is the impact of free water renal excretion rates on the development of hyponatremia?

Response: Thank you, we agree that this is an important point. We have added specific discussion on this point in both the Introduction as well as the Discussion.

Comment #35: What about the likely confounding variables that induce SIADH and the development of hyponatremia??

Response: Thank you, we agree that this is an important point. We have added specific discussion on this point in both Introduction to cover this point.

Comment #36: Since most of your cohort studies involved clear non-osmotic stimuli to AVP secretion (anti-psychotic medications, stress, exercise, etc.) this section warrants an extensive revision.

Response: Thank you, we agree that this is an important point. We have introduced more discussion on this topic in both Introduction and Discussion sections.

Comment #37: In fact, all four of your main conclusions require critical reflection with regards to the vast pathophysiological significance of your findings to more comprehensively enhance our broader understanding of this topic.

Response: Thank you, we agree with you, and consequently revised the manuscript extensively including the conclusion and hope that these revisions provide a more comprehensive understanding of this topic.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Topliss, Duncan Alfred Health, Endocrinology & Diabetes
<b>REVIEW RETURNED</b>	01-Aug-2021

<b>GENERAL COMMENTS</b>	The extensive revision of the MS undertaken in response to the reviewers' comments is satisfactory to this reviewer.  There are some typographical errors remaining which could readily be detected and removed by a spell check program being applied.
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<b>REVIEWER</b>	Ito, Hiroshi University of Tsukuba, Division of Hospital Medicine
<b>REVIEW RETURNED</b>	30-Jul-2021

<b>GENERAL COMMENTS</b>	Thank you very much for giving me a chance of reviewing your manuscript. This manuscript is a literature review of hyponatremia secondary to water intoxication. Compared to the original version, this revised version seems improved in that the information on the etiology of water intoxication is described more clearly. In addition, the characteristics of each etiology are written in detail, which would help readers see patients with water intoxication.  This literature review is based mainly on case reports. Therefore, I have to point out that the data presented in this manuscript does not necessarily reflect the true prevalence of each etiology. The authors should clarify this limitation in the discussion section.  Please refer to other referees about the expression of the manuscript and statistics because I am not an English speaker or statistician.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Hiroshi Ito, University of Tsukuba

Comments to the Author:

Thank you very much for giving me a chance of reviewing your manuscript. This manuscript is a literature review of hyponatremia secondary to water intoxication. Compared to the original version, this revised version seems improved in that the information on the etiology of water intoxication is described more clearly. In addition, the characteristics of each etiology are written in detail, which would help readers see patients with water intoxication. This literature review is based mainly on case reports. Therefore, I have to point out that the data presented in this manuscript does not necessarily reflect the true prevalence of each etiology. The authors should clarify this limitation in the discussion section. Please refer to other referees about the expression of the manuscript and statistics because I am not an English speaker or statistician.

Reply: Agree, comment added to the Discussion (see paragraph on Strengths and Limitations (page 23 of the Main Document – marked; paragraph 1, lines 2-3)

Reviewer: 1

Prof. Duncan Topliss, Alfred Health

Comments to the Author:

The extensive revision of the MS undertaken in response to the reviewers' comments is satisfactory to this reviewer.

There are some typographical errors remaining which could readily be detected and removed by a spell check program being applied.

Reply: Agree. The manuscript has been carefully proof-read and minor typographical errors and grammar have been corrected.