PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The hidden sodium in effervescent-tablet dietary supplements and over-the-counter drugs: a comparative cross-sectional study
AUTHORS	Kunz , Michael; Götzinger, Felix; Jacobs, Cathy M.; Lauder, Lucas; Ukena, Christian; Meyer, Markus; Laufs, Ulrich; Schulz, Martin; Böhm, Michael; Mahfoud, Felix

VERSION 1 – REVIEW

REVIEWER	Adedayo E. Ojo University of Abuja Teaching Hospital, Department of Internal Medicine
REVIEW RETURNED	10-Aug-2023

GENERAL COMMENTS	Overall, the paper has the potential to make a significant contribution to the field and will undoubtedly stimulate meaningful discussions among researchers and practitioners alike. The conclusion and discussion sections provided insightful reflections on the implications of the study, suggesting avenues for further actions. However, there are a few facets of the study that could benefit from further attention and refinement. Study design should be mention in the abstract and in the main methods. The researchers measured the sodium content of different types of effervescent tablets (both dietary supplements and over-the-counter drugs) available in Germany and the US and compared their sodium content but the study design was not mentioned (this should be a “comparative cross-sectional study”) In general, the statistical methods provided sufficient detail for readers to understand the data analysis methods employed and how statistical significance was determined. The authors ensured that the statistical tests are appropriate for the study's objectives. However, if there are any specific assumptions made for the tests, such as the assumption of equal variances for ANOVA, it would be beneficial to mention them explicitly. Another potential ‘minor error’ in the provided statistical analysis plan is the inconsistency in mentioning two different post hoc methods: "Dunn-Bonferroni" and "Bonferroni." The text mentions "Dunn-Bonferroni" as the post hoc method for pairwise comparisons after significant ANOVA or Kruskal-Wallis tests, but later, it refers to "Bonferroni" when mentioning the significance level. In the conclusion section (Lines 13-18): the word "abstain" in the context of advising patients at risk- the term "abstain" implies complete avoidance or cessation. However, considering the severity of the situation, it might be more appropriate to suggest "reconsider" or "limit" the use of effervescent tablets instead of suggesting

	complete avoidance, as the latter may not be feasible for all patients. References: Update references 2,5 and 10 to more recent studies. References 15, 16, 17 and 18 need to be correctly formatted

REVIEWER	N. Nani National Defence University of Malaysia, Faculty of Medicine and Defence Health
REVIEW RETURNED	16-Aug-2023

GENERAL COMMENTS	Overall , clearly written. Easy to understand. 1.Some unit for sodium content need to be clarified (mg/tablet) or just (mg) 2.Are the data used for the sodium content from the measured sodium content or derived from the product label or the combination of both? Its good to have information on the comparison between the measured sodium with what was claimed in the label. 3. No ethical issue is foreseen in this project. However, it is advisable to have a proper ethical clearance from any established ethical committee. 4. Some calculation for percentage are not quite clear.

REVIEWER	Sebastiano Lava University Children's Hospital Bern-University of Bern
REVIEW RETURNED	18-Aug-2023

GENERAL COMMENTS	Kunz and colleagues propose an interesting study addressing the “hidden” sodium content in effervescent tables. They measured the sodium content of 39 dietary supplements and assessed the sodium content declared on the SmPC of 33 over-the-counter effervescent tablets. They also assessed the sodium content declared on the leaflet of 51 dietary supplements effervescent tablets sold in the USA. The study is academically interesting and bears some relevant clinical-epidemiological implications. The design is adequate to the study question. The study appears to have been carefully performed. The conclusions are globally sound with the obtained results, but Authors need to add one important interpretation point regarding potential impact on blood pressure and cardiovascular health with respect to duration of intake (i.e. 5 days very-high sodium intake through a cough-and-cold medicine may have much less impact on BP and cardiovascular risk than 365 days of moderate sodium intake through a dietary supplement, see specific comment below). Another point, which should be briefly addressed in the discussion is that also prescription medications may contain sodium, and that the key point in any drug intake (including OTC and dietary supplements) is a favorable risk/benefit balance. It is important to build a culture of risk/benefit balance that englobes not only prescription medicines, but also OTC’s and dietary supplements. This study is actually a good example of why this is important (please see specific comment below). The manuscript is globally well structured and written in a good English. However, it should be shortened by approximately 10-15% of its current length. Peer-reviewed references are appropriate and well-chosen. However, currently, 10 out of 31 references are not

	peer-reviewed. Authors must reduce non peer-reviewed references to a maximum of n=4, either by substituting them with peer-reviewed publications or simply by deleting them. The figures are clear. The tables are a bit heavy, but still clear to read. Following specific comments and requests should be addressed and, I hope, they should help the Authors in improving the quality of their manuscript. (CAVE: Page numbers refer to the pdf file (not to the printed numbers, which are partially inconsistent, for example: page 5 of the pdf has “Page 4 of 37” printed in the top right and page number “2” printed in the bottom right, such page is referenced as “page 5” in my review report here below).) Abstract, page 5 of the pdf, lines 21-27: and compared to the measured one? Or are you here referring to the US tablets? Page 5, line 30/31: “in the US.” -> “in the United States of America.” Page 5 of the pdf, lines 35-38: are these values based on the drug label information or on the optical emission spectrometry with argon plasma? If I understand correctly, these values were measured. It may be useful, for clarity to the Readership, to formulate the sentence so to make this clear, for example: “The measured sodium content in the dietary supplements available in Germany was 283.9±122.6 mg sodium/tablet, …” Page 5, lines 47-48: “The sodium content in products available in Germany was higher when compared to those in the US ($p<0.001$)” -> “The sodium content measured in products available in Germany was higher when compared to the sodium content declared on the label of the products sold in the USA ($p<0.001$).” Page 5, lines 49-51: “The median sodium content of a single dosage of the OTC drugs was” -> “The median SmPC-declared sodium content of a single dose of the OTC drugs was” Page 6, lines 8-13: “Patients with sodium-sensitive conditions such as hypertension and heart failure should avoid effervescent tablets.” -> “While waiting for such transparent information, patients with sodium-sensitive conditions such as fluid overload syndromes, hypertension and heart failure should avoid effervescent tablets.” Page 8, lines 18-21 (“Products with main active ingredients other than those of the above categories have been grouped under “other products”.”): delete. Page 8, lines 44-47: Why not the whole tablet? If your aim was to quantify the amount of sodium contained in one tablet...this should have be done instead. Am I wrong? Page 9, lines 5-11: Is this sentence needed? What does this sentence add? Consider deleting this sentence (which would also help you to achieve the shortening of the manuscript by 10-15% that I have requested above).

	Page 9, lines 43-46 (“Further, we analyzed the aggregate amount of dispensed packages”): Sorry, I do not understand: what does this add to the DDD? Why was this necessary? You were aiming at identifying the sodium content of tablets, not the amount overall consumed by the population (epidemiological study), right? Page 9, line 57 (“aggregated mail-order sales’ data.“): aggregated from what? How (criterion)? Why? Page 10, line 22/23: “categories have been grouped” -> “categories were grouped” Page 10, lines 49-52 (“Patients and the public were not involved in any way so a patient and public involvement statement is not applicable.”): delete. Page 11, lines 9-13: this is based on the measures you performed, not on the product label, right? Please specify it here for clarity. Page 11, lines 35-38: this means that all the values provided above are derived from the measurements you performed, right? Did you perform a comparison, for the 5 products providing sodium content information on their label, between sodium declared on the product label and measured sodium content? This may be interesting (and may help interpreting the comparison with the USA data). Page 11, line 41: “in the US” -> “in the United States of America” Page 11, lines 56-59: are you comparing measured (Germany) versus declared (USA), or declared in Germany vs declared in the USA? The second comparison would detect national differences, the first cannot differentiate between national differences and differences between measured and declared content. Page 12, line 3: here you are referring to the sodium content declared on the SmPC of the OTC drugs, right? It may be worth explicitly stating this to make it clear to the Readership. For example, you might reformulate the first sentence (line 3) as follows: “The sodium content declared on the SmPC of the OTC drugs sold in Germany is listed in table 3.” Page 12, lines 44-55: Either delete or provide this information in a separate paragraph (ideally, under Introduction or, even better, Discussion). Since you should shorten your manuscript by 10-15% of its current length, I suggest you to simply delete these lines. Page 13, lines 33-38: see comment above (relating to Page 11, lines 56-59): comparing the 5 products (13%) with label information to the USA data (or comparing all the measured sodium contents from Germany with the label information provided in the USA)? Otherwise, the comparison may return label vs measured rather than USA vs Germany. Page 13, line 57 (“Against this background”): Why "against"? Such an initiative should rather be supported and praised by the WHO! Page 14, lines 6-8: “which may, in part, aggravated by hidden” -> “in part, be aggravated by hidden” Page 15, lines 5-8: please also provide the 95%-CI of the adjusted

	OR listed (e.g. “1.16” -> “1.16 (95%-CI … - …)”). Page 15, line 10 (“in this study”): from reference #24 or from your study? If Ref. #24, "this" -> "that" (or "this latter"). If yours, insert one (or more) sentence(s) (currently, it would lack a bit a link between lines 3- 8 and lines 9-11). Pag 15, line 34: and of the grocery store drugs? Please provide the 2 tablets with highest sodium content also for that category. Page 16, lines 12-20 (“The exposure to…” up to “…in fall and winter.”): delete. Page 16, line 46: “applied” -> “administered” or “taken”. Page 17, lines 3-8: in Germany, in Europe or worldwide? Page 17, lines 8-10 (“This amount of sodium is already contained in approximately 3 of the included effervescent vitamin tablets.”): in one single tablet of three specific examples, or in n=3 tablets of one specific example? Please specify. Page 17, lines 12-15 (“9 million cardiovascular Events”): in China or worldwide? Please specify. Two further points should be addressed in the revised Discussion. 1) Following discussion, putting the issue in the context, should be added: one sodium-rich dietary supplement tablet 1x/d for the whole year, over several years, can increase BP and the cardiovascular risk. However, 1-2 tablets a day of a sodium-rich cough & cold drug, taken for 3-4 days (typical duration of common cold symptoms requiring a tablet), are pretty unlikely to lead to such an increase, even if their sodium content is higher. Epidemiology and population risk reduction act over long periods of time. The difference between integrator/dietary supplements (which may have a lower sodium content but are usually taken throughout the year, or at least over one season) and common cold/cough OTC effervescent tablets taken for 3-4 days should be discussed. 2) Another aspect to mention and to address in the Discussion section is that also some prescription medicines contain sodium. Of course, they may be life-saving and needed, and nobody would ever propose to avoid them because of their sodium content (among the several excipients any tablet contains). The key point, which should be made clear and stressed in the Discussion, is that the rationale for any drug intake (including dietary supplements and OTC drugs) should always be a risk/benefit balance. This study shows how important is that the same approach should apply also for OTC and dietary supplements. Indeed, this is probably the key message and conclusion of your study: dietary supplements are sometimes regarded as "sweets" / “candies”, but should be actually seen as drugs. The question should always be asked: is there a proven benefit? Is there any side effect (including sodium content)? What is the risk/benefit balance for this specific patient in this particular situation (or period of life)? Of course, this judgment may be difficult for the public (especially under the pressure of publicity and marketing initiatives). This discussion should be integrated in the manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Overall, the paper has the potential to make a significant contribution to the field and will undoubtedly stimulate meaningful discussions among researchers and practitioners alike. The conclusion and discussion sections provided insightful reflections on the implications of the study, suggesting avenues for further actions. However, there are a few facets of the study that could benefit from further attention and refinement.

1. Study design should be mention in the abstract and in the main methods. The researchers measured the sodium content of different types of effervescent tablets (both dietary supplements and over-the-counter drugs) available in Germany and the US and compared their sodium content but the study design was not mentioned (this should be a “comparative cross-sectional study”)

Author response:

Thank you for this important advice which we implemented. We changed the following parts and added the section “study design” in the main methods:

Title: The hidden sodium in effervescent tablets of dietary supplements and over-the-counter drugs – A comparative cross-sectional study

Abstract: Design: Comparative cross-sectional study.

Methods: Study design

A comparative cross-sectional study was conducted in 2022 and 2023 to examine and compare the sodium content of different categories of effervescent tablets.

[…]

Classification and data source of the dietary supplements available in the United States of America

The sodium content of 51 dietary supplement effervescent tablets available in the United States of America was derived in May 2023 from the Dietary Supplement Label Database.

2. In general, the statistical methods provided sufficient detail for readers to understand the data analysis methods employed and how statistical significance was determined. The authors ensured that the statistical tests are appropriate for the study's objectives. However, if there are any specific assumptions made for the tests, such as the assumption of equal variances for ANOVA, it would be beneficial to mention them explicitly. Another potential ‘minor error’ in the provided statistical analysis plan is the inconsistency in mentioning two different post hoc methods: "Dunn-Bonferroni" and "Bonferroni." The text mentions "Dunn-Bonferroni" as the post hoc method for pairwise comparisons after significant ANOVA or Kruskal-Wallis tests, but later, it refers to "Bonferroni" when mentioning the significance level.

Author response:

We have tested all the assumptions for ANOVA. We revised the part Statistical methods:

The data are presented as means □ standard deviation (SD), medians and interquartile ranges (IQR), or numbers (%). Normal distribution was tested using Kolmogorov-Smirnov/ Shapiro-Wilk test and using a histogram. Analysis of variance (ANOVA) was used (after tested for all assumptions for ANOVA: normally distribution, independence of cases, homogeneity of variance) for comparisons of normally distributed parameters, and for comparisons between non-normally distributed parameters, the Kruskal-Wallis test was used. If these tests were significant, we used a post hoc method (Dunn-Bonferroni) for pairwise comparisons. For comparisons between two non-normally distributed parameters, the Mann-Whitney-U-test was used. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS (version 27.0.1.0). Data sharing: All data relevant to the study are included in the article or uploaded as supplementary information.

3. In the conclusion section (Lines 13-18): the word "abstain" in the context of advising patients at risk- the term "abstain" implies complete avoidance or cessation. However, considering the severity of the situation, it might be more appropriate to suggest "reconsider" or "limit" the use of effervescent tablets instead of suggesting complete avoidance, as the latter may not be feasible for all patients.

Author response:
Thank you this comment. We have changed the wording accordingly.
Based on the study findings, patients at risk should be advised to limit effervescent tablets to prevent the ingestion of hidden sodium.

4. Update references 2,5 and 10 to more recent studies.

Author response:
We updated the mentioned references in the following way:
Deleted: reference 2 Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected Effect of Dietary Salt Reductions on Future Cardiovascular Disease. N Engl J Med 2010;362:590–9. doi:10.1056/NEJMoa0907355
and reference 5 He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. Lancet 2011;378:380–2. doi:10.1016/S0140-6736(11)61174-4
Replaced by: Salt Reduction to Prevent Hypertension and Cardiovascular Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Feb 18;75(6):632-647. doi: 10.1016/j.jacc.2019.11.055
and Role of salt intake in prevention of cardiovascular disease: controversies and challenges. Nat Rev Cardiol. 2018 Jun;15(6):371-377. doi: 10.1038/s41569-018-0004-1

Deleted: reference 10 Brown IJ, Tzoulaki I, Candeias V, et al. Salt intakes around the world: implications for public health. Int J Epidemiol 2009;38:791–813. doi:10.1093/ije/dyp139
Replaced by: Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24-h urinary sodium excretion and dietary surveys worldwide. BMJ open. 2013 doi: 10.1136/bmjopen-2013-003733

5. References 15, 16, 17 and 18 need to be correctly formatted

Author response:
In reconsidering their relevance and also comment 1 by reviewer #3, the references 15-18 were deleted.

Reviewer 2
Overall , clearly written. Easy to understand.

1. Some unit for sodium content need to be clarified (mg/tablet) or just (mg)

Author response:
Thank you. We clarified the following parts:
Discussion: This study assessed the sodium content of nutritional supplement effervescent tablets available in Germany and found the sodium amount to range from 76.0 mg/tablet to 564.7 mg/tablet (average 283.9 mg/tablet) representing up to 28% of the maximum recommended daily sodium intake.
[…]
Products available in the United States of America also contain a relevant amount of sodium with contents ranging from 40 to 360 mg/tablet.
[…]

Herein, the average sodium content of effervescent food supplements tablets in Germany was 283.9 mg/tablet, and the median sodium content of the pharmacy-only effervescent tablets was 157.0 mg/tablet.

2. Are the data used for the sodium content from the measured sodium content or derived from the product label or the combination of both? Its good to have information on the comparison between the measured sodium with what was claimed in the label.

Author response:
The specified sodium content of the dietary supplement effervescent tablets available in Germany are actually the measured sodium content via ICP-OES whereas the specified sodium content of the dietary supplement effervescent tablets available in the US and the OTC drugs was obtained from the summary of product characteristics or package inserts.
The comparison of the measured and the claimed sodium content is an important point but only 5 products of the dietary supplement effervescent tablets available in Germany declared their sodium content on the label. The measured and claimed sodium amounts of these 5 products were identical.
We added the following part to clarify this:
Results: Only 5 (12.8%) products (all of the Mivolis brand) declared the sodium content on the packaging which was nearly identical to the measured sodium content.

3. No ethical issue is foreseen in this project. However, it is advisable to have a proper ethical clearance from any established ethical committee.

Author response:
This study did not require approval of ethic committees as no patients or animals were involved.

4. Some calculation for percentage are not quite clear.

Author response:
Please see our answers below.
Your comment: How do you calculate 1/5 th (19%/23%)?Based on which sodium content?
The included vitamin products contain an average of 378.3 mg sodium/tablet and the median sodium content of the included pain/common cold drugs was 452.1 mg sodium/tablet. The World Health Organization (WHO) recommends reducing sodium intake to <2,000 mg/day. Consequently, consuming one of the included effervescent vitamin tablets or pain/common cold tablets corresponds to about one fifth (19%/23%) of the maximum recommended daily sodium intake.

Additional comments from the attached file:
5. Did you compare the sodium ammount declared with the amount measured?

Author response:
Yes, this is explained more in detail in author response 2.

6. Do you mean WHO recommend that a single effervescent tablet should contain 4-38% MRDSI? This sentence requires reconstruction.

Author response:
We have revised the text as follows.
Results: Based on the recommended maximum intake of 2,000 mg sodium/day [9], a single effervescent tablet contained as much as 4-28% of the maximum recommended daily sodium intake.

7. What do you mean by relevant amount?

Author response:
We think, that approximately 10% of the maxium recommended daily sodium intake (200 mg sodium) is a relevant amount of sodium because patients cover a tenth of their daily sodium requirement with one effervescent tablet. Due to the already high daily sodium intake worldwide, these amounts of additional “hidden” sodium may contribute to poor blood pressure control, cardiovascular events, including hospitalization for acute heart failure and death.

Reviewer 3
Kunz and colleagues propose an interesting study addressing the “hidden” sodium content in effervescent tables. They measured the sodium content of 39 dietary supplements and assessed the sodium content declared on the SmPC of 33 over-the-counter effervescent tablets. They also assessed the sodium content declared on the leaflet of 51 dietary supplements effervescent tablets sold in the USA.

The study is academically interesting and bears some relevant clinical-epidemiological implications. The design is adequate to the study question. The study appears to have been carefully performed. The conclusions are globally sound with the obtained results, but Authors need to add one important interpretation point regarding potential impact on blood pressure and cardiovascular health with respect to duration of intake (i.e. 5 days very-high sodium intake through a cough-and-cold medicine may have much less impact on BP and cardiovascular risk than 365 days of moderate sodium intake through a dietary supplement, see specific comment below). Another point, which should be briefly addressed in the discussion is that also prescription medications may contain sodium, and that the key point in any drug intake (including OTC and dietary supplements) is a favorable risk/benefit balance. It is important to build a culture of risk/benefit balance that englobes not only prescription medicines, but also OTC’s and dietary supplements. This study is actually a good example of why this is important (please see specific comment below).

The manuscript is globally well structured and written in a good English. However, it should be shortened by approximately 10-15% of its current length. Peer-reviewed references are appropriate and well-chosen. However, currently, 10 out of 31 references are not peer-reviewed. Authors must reduce non peer-reviewed references to a maximum of n=4, either by substituting them with peer-reviewed publications or simply by deleting them.

The figures are clear. The tables are a bit heavy, but still clear to read.

Following specific comments and requests should be addressed and, I hope, they should help the Authors in improving the quality of their manuscript.

Author response:
Thank you very much for these constructive comments, helping to further improve the quality of the manuscript. We have shortened the manuscript and revised the references (the following references and sentences were deleted):
7 Götzinger F, Kunz M, Lauder L, et al. Arterial hypertension - clinical trials update 2022. Hypertens Res 2022;32:21–31. doi:10.1038/s41440-022-00931-2
15 Fachinformation. https://www.fachinfo.de
16 Deutsches Arzneiprüfungsinstitut e.V. https://www.dapi.de
17 INSIGHT Health GmbH & Co. KG. https://www.insight-health.de/
18 DatamedIQ GmbH. https://www.datamediq.com/

Patients with sodium-sensitive conditions such as hypertension and heart failure should avoid effervescent tablets.

Products with main active ingredients other than those of the above categories have been grouped under “other products”.
Drugs with an active ingredient other than those of the above categories have been grouped under “other products”.
Regarding blank and reference solutions signals and the resulting linear calibration curve, sodium content in all different effervescent tablets was determined. Details to measurement accuracy of the method can be found elsewhere.[14]
The INSIGHT Health database includes extrapolated data from a representative sample of over 5,800 community pharmacies.[17] The DatamedIQ database provides aggregated mail-order sales' data.[18]
Products with an active ingredient other than those of the above categories have been grouped under “other products”.
A total of 3.96 million packs of the included pain/common cold drugs and 5.30 million packs of the included cough drugs were sold in German pharmacies and via mail-order in 2021 (table 3).[17,18] In 2021, a total of 52.32 million defined daily doses of prescribed calcium/vitamin D drugs, mainly as effervescent tablets, have been dispensed to the expense of the SHI funds in German community pharmacies.[20]
The exposure to effervescent tablets was estimated using a questionnaire that possibly underestimated the actual consumption.[13] The study was performed in spring/summer, and the intake of effervescent tablets could vary seasonally with an increase during the season of common colds in fall and winter.

1. Abstract, page 5 of the pdf, lines 21-27: and compared to the measured one? Or are you here referring to the US tablets?

Author response:
We have revised the abstract as follows.
Setting and Methods: The sodium content of 39 dietary supplement effervescent tablets available in Germany was measured using optical emission spectrometry with inductively coupled argon plasma. The sodium content of 33 common pharmacy-only effervescent tablets (“over-the-counter (OTC) drugs”) in Germany was obtained from the summary of product characteristics. We compared the sodium content of the measured German dietary supplement effervescent tablets to that of 51 dietary supplement effervescent tablets available in the United States of America (data: National Institutes of Health's Dietary Supplement Label Database).

2. Page 5, line 30/31: “in the US.” -> “in the United States of America.”

Author response:
Done.
We compared the sodium content of the measured German dietary supplement effervescent tablets to that of 51 dietary supplement effervescent tablets available in the United States of America (data: National Institutes of Health's Dietary Supplement Label Database).

3. Page 5 of the pdf, lines 35-38: are these values based on the drug label information or on the optical emission spectrometry with argon plasma? If I understand correctly, these values were measured. It may be useful, for clarity to the Readership, to formulate the sentence so to make this clear, for example: “The measured sodium content in the dietary supplements available in Germany was 283.9±122.6 mg sodium/tablet, …”

Author response:
This is correct, these values were measured with ICP-OES. Thank you for this suggestion.

The measured sodium content in the German dietary supplements was 283.9±122.6 mg sodium/tablet, equivalent to 14□6% of the maximum recommended daily sodium intake (MRDSI).

4. Page 5, lines 47-48: “The sodium content in products available in Germany was higher when compared to those in the US (p<0.001)” -> “The sodium content measured in products available in Germany was higher when compared to the sodium content declared on the label of the products sold in the USA (p<0.001).”

Author response:
Thank you, this was changed accordingly.
The sodium content measured in products available in Germany was higher when compared to the declared sodium content on the label of the products sold in the United States of America (p<0.001).

5. Page 5, lines 49-51: “The median sodium content of a single dosage of the OTC drugs was” -> “The median SmPC-declared sodium content of a single dose of the OTC drugs was”

Author response:
Thank you, this was changed accordingly.
The median summary of product characteristics-declared sodium content of a single dose of the German OTC drugs was 157.0 mg (interquartile range (IQR): 98.9-417.3 mg); pain/common cold drugs contained the most sodium (median: 452.1 mg; IQR: 351.3-474.0 mg).

6. Page 6, lines 8-13: “Patients with sodium-sensitive conditions such as hypertension and heart failure should avoid effervescent tablets.” -> “While waiting for such transparent information, patients with sodium-sensitive conditions such as fluid overload syndromes, hypertension and heart failure should avoid effervescent tablets.”

Author response:
To further shorten the text, as suggested, this sentence was deleted.
Patients with sodium-sensitive conditions such as hypertension and heart failure should avoid effervescent tablets.

7. Page 8, lines 18-21 (“Products with main active ingredients other than those of the above categories have been grouped under “other products”.”): delete.

Author response:
We deleted the sentence and another one from the next part:
Products with main active ingredients other than those of the above categories have been grouped under “other products”.
[…]
Drugs with an active ingredient other than those of the above categories have been grouped under “other products”.

8. Page 8, lines 44-47: Why not the whole tablet? If your aim was to quantify the amount of sodium contained in one tablet...this should have be done instead. Am I wrong?

Author response:
Due to possible variations in sodium content of effervescent tablet of a specific product, all effervescent tablets of one package (in most cases 10 to 20) were ground up. Then the powder was carefully mixed and a sample amount corresponding to the expected sodium content was calculated. The sodium content was calculated for one tablet. This was done to avoid “choosing” a tablet with a particularly high or particularly low sodium content for analysis from a package.

9. Page 9, lines 5-11: Is this sentence needed? What does this sentence add? Consider deleting this sentence (which would also help you to achieve the shortening of the manuscript by 10-15% that I have requested above).

Author response:
Done.
Regarding blank and reference solutions signals and the resulting linear calibration curve, sodium content in all different effervescent tablets was determined. Details to measurement accuracy of the method can be found elsewhere.[14]

10. Page 9, lines 43-46 ("Further, we analyzed the aggregate amount of dispensed packages"): Sorry, I do not understand: what does this add to the DDD? Why was this necessary? You were aiming at identifying the sodium content of tablets, not the amount overall consumed by the population (epidemiological study), right?

Author response:
On the one hand, we aimed to investigate the sodium content of effervescent tablets and on the other hand we wanted to show that OTC drugs and dieaty supplement effervescent tablets are frequently sold and consumed by a relevant proportion of the population. Hence, we investigated and provided the amount of effervescent tablets sold in pharmacies because the quantity of dietary supplement effervescent tablets from discounters, grocery- and drugstores is not publicly available. But certainly, more of these products are sold in discounters, grocery- and drugstores than in pharmacies.

11. Page 9, line 57 ("aggregated mail-order sales' data."): aggregated from what? How (criterion)? Why?

Author response:
To further shorten the manuscript, we deleted the following two sentences (but we added the data sources in the text):
The INSIGHT Health database includes extrapolated data from a representative sample of over 5,800 community pharmacies.[17] The DatamedIQ database provides aggregated mail-order sales' data.[18]
Further, we analyzed the aggregate amount of dispensed packages of drugs and diet supplements as effervescent tablets in community pharmacies and via mail-order using dispensing data reimbursed by SHI funds as well as private health insurance companies and over-the-counter sales from the INSIGHT Health (https://www.insight-health.de/) and DatamedIQ (https://www.datamediq.com/) databases, respectively.

12. Page 10, line 22/23: "categories have been grouped" -> "categories were grouped"

Author response:
In order to shorten the manuscript, we deleted the two sentences above (your comment 7) and this one.
Products with an active ingredient other than those of the above categories have been grouped under "other products".

13. Page 10, lines 49-52 ("Patients and the public were not involved in any way so a patient and public involvement statement is not applicable."): delete.

Author response:
This is a requirement from the Journal. So, we have to add the following part:

Patient and public involvement
None.

14. Page 11, lines 9-13: this is based on the measures you performed, not on the product label, right? Please specify it here for clarity.

Author response:
Correct, I hope we clarified it by adding the following statement.
The sodium content of the effervescent tablets measured by ICP-OES is listed in table 1.

15. Page 11, lines 35-38: this means that all the values provided above are derived from the measurements you performed, right? Did you perform a comparison, for the 5 products providing sodium content information on their label, between sodium declared on the product label and measured sodium content? This may be interesting (and may help interpreting the comparison with the USA data).

Author response:
Yes, this is correct, all the values provided in the part “Dietary supplement effervescent tablets in Germany” are derived from the measurements we performed. The measured and claimed sodium amounts of these 5 products were nearly identical. We added the following sentence to the manusript:
Results: Only 5 (12.8%) products (all of the Mivolis brand) declared the sodium content on the packaging which was nearly identical to the measured sodium content.

16. Page 11, line 41: “in the US” -> “in the United States of America”

Author response:
We replaced the abbreviation US to United States of America:
Dietary supplement effervescent tablets in the United States of America

17. Page 11, lines 56-59: are you comparing measured (Germany) versus declared (USA), or declared in Germany vs declared in the USA? The second comparison would detect national differences, the first cannot differentiate between national differences and differences between measured and declared content.

Author response:
Here we are comparing measured (Germany) sodium contents with declared (USA). Assuming the manufacture declares the correct sodium content on the packing (which we should take for granted, otherwise it would be fraud), we think, that the detection of national differences is possible. Nevertheless, we agree that this is a limitation. It is not guaranteed that the ingredients declared on the packing are “correct” (references: Dietary Supplement Ingredient Database (DSID) and the Application of Analytically Based Estimates of Ingredient Amount to Intake Calculations. J Nutr 2018;148:1413S–1421S. doi:10.1093/jn/nxy092. and Quantity of Melatonin and CBD in Melatonin Gummies Sold in the US JAMA 2023. doi: 10.1001/jama.2023.2296 and Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings. JAMA Network Open. 2018;1(6):e183337. doi:10.1001/jamanetworkopen.2018.3337). We corrected and clarified this part and added a part in Limitations:
The measured sodium content of dietary supplements available in Germany was higher when compared with the declared sodium content of products available in the United States of America ($p<0.001$).
Limitations
Measured (Germany) sodium contents of dietary supplements were compared with declared (United States of America). Assuming the manufacture declares the correct sodium content on the packing,

the detection of national differences is possible. Nevertheless, the assumption that the declared sodium content of dietary supplements available in the United States of America are valide, is a limitation. It is not guaranteed that the ingredients declared on the packing are “correct” (references: Dietary Supplement Ingredient Database (DSID) and the Application of Analytically Based Estimates of Ingredient Amount to Intake Calculations. J Nutr 2018;148:1413S–1421S. doi:10.1093/jn/nxy092. and Quantity of Melatonin and CBD in Melatonin Gummies Sold in the US JAMA 2023. doi: 10.1001/jama.2023.2296 and Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated With US Food and Drug Administration Warnings. JAMA Network Open. 2018;1(6):e183337. doi:10.1001/jamanetworkopen.2018.3337).

18. Page 12, line 3: here you are referring to the sodium content declared on the SmPC of the OTC drugs, right? It may be worth explicitly stating this to make it clear to the Readership. For example, you might reformulate the first sentence (line 3) as follows: “The sodium content declared on the SmPC of the OTC drugs sold in Germany is listed in table 3.”

Author response:
This is correct, the sodium contents of the OTC drugs were derived from the SmPC. Your reformulation is perfect to clarify this.
The sodium content declared on the summary of product characteristics of the OTC drugs sold in Germany is listed in table 3.

19. Page 12, lines 44-55: Either delete or provide this information in a separate paragraph (ideally, under Introduction or, even better, Discussion). Since you should shorten your manuscript by 10-15% of its current length, I suggest you to simply delete these lines.

Author response:
Thank you, this is correct. We discussed the sales figures later in the Discussion, so we deleted this part here:
A total of 3.96 million packs of the included pain/common cold drugs and 5.30 million packs of the included cough drugs were sold in German pharmacies and via mail-order in 2021 (table 3).[17,18] In 2021, a total of 52.32 million defined daily doses of prescribed calcium/vitamin D drugs, mainly as effervescent tablets, have been dispensed to the expense of the SHI funds in German community pharmacies.[20]

20. Page 13, lines 33-38: see comment above (relating to Page 11, lines 56-59): comparing the 5 products (13%) with label information to the USA data (or comparing all the measured sodium contents from Germany with the label information provided in the USA)? Otherwise, the comparison may return label vs measured rather than USA vs Germany.

Author response:
As we mentioned above, we are comparing measured (Germany) sodium contents with declared (USA). This has been further clarified in the text. Assuming the manufactures declare the correct sodium content on the packing, we think, that the detection of national differences is possible.
Correction in terms of standardization:
Products available in the United States of America also contain a relevant amount of sodium (ranging from 40 to 360 mg/tablet). Of note, dietary supplement effervescent tablets available in Germany contained more sodium than declared in those available in the United States of America. This may, in part, be related to selection bias since only a few manufactures from the United States of America voluntarily provide information about the sodium content.

21. Page 13, line 57 (“Against this background”): Why "against"? Such an initiative should rather be supported and praised by the WHO!

Author response:
We rephrased this part:
Consequently, the WHO recommends that daily sodium intake should not exceed 2,000 mg.

22. Page 14, lines 6-8: “which may, in part, aggravated by hidden” -> “in part, be aggravated by hidden”

Author response:
Thank you pointing out the grammatical error:
Nonetheless, the daily sodium intake around the world is often much higher (9,000-12,000 mg table salt/day; 3,500-7,700 mg sodium/day), which may, in part, be aggravated by hidden sodium consumption.

23. Page 15, lines 5-8: please also provide the 95%-CI of the adjusted OR listed (e.g. “1.16” -> “1.16 (95%-CI … - …)”).

Author response:
We deliberately omitted the CI in order to shorten the text. But of course, we can provide the 95%-CI:
The adjusted odds ratio for exposure to sodium-containing drugs were 1.16 (95%-confidence interval (95%-CI): 1.12-1.21) for the composite of myocardial infarction, stroke, or vascular death, 1.28 (95%-CI: 1.23-1.33) for all-cause mortality, and 7.18 (95%-CI: 6.74-7.65) for hypertension.

24. Page 15, line 10 (“in this study”): from reference #24 or from your study? If Ref. #24, "this" -> "that" (or "this latter"). If yours, insert one (or more) sentence(s) (currently, it would lack a bit a link between lines 3- 8 and lines 9-11).

Author response:
Correction:
Of note, the sodium content of some of the included effervescent tablets in this study is comparable with the sodium content of the drugs included in the mentioned study (reference 24). Consequently, the consumption of effervescent tablets investigated herein may contribute to an increased cardiovascular risk.

25. Pag 15, line 34: and of the grocery store drugs? Please provide the 2 tablets with highest sodium content also for that category.

Author response:
We added the following part:
Six products (8.3%) contained more than 500 mg sodium/tablet, Vitamin C 1000® (fit+Vital) and Vitamin C+Zink+Selen+Vitamin D3® (elkos Vivede) had the highest amount of sodium/tablet (564.7 mg and 541.1 mg) of the dietary supplements available in Germany.

26. Page 16, lines 12-20 (“The exposure to…” up to “…in fall and winter.”): delete.

Author response:
We deleted the following part to shorten the manuscript:
The exposure to effervescent tablets was estimated using a questionnaire that possibly underestimated the actual consumption.[13] The study was performed in spring/summer, and the intake of effervescent tablets could vary seasonally with an increase during the season of common colds in fall and winter.

27. Page 16, line 46: “applied” -> “administered” or “taken”.

Author response:
Thank you.
Various sodium-containing drugs administered as effervescent tablets are available.

28. Page 17, lines 3-8: in Germany, in Europe or worldwide?

Author response:
An important notice, these figures refer to the population of the United States of America.
A dietary reduction of 1,200 mg sodium/day could translate into an annual reduction of 60,000-120,000 new coronary heart disease patients, 32,000-66,000 fewer strokes, and 54,000-99,000 fewer myocardial infarctions in the United States of America.

29. Page 17, lines 8-10 (“This amount of sodium is already contained in approximately 3 of the included effervescent vitamin tablets.”): in one single tablet of three specific examples, or in n=3 tablets of one specific example? Please specify.

Author response:
Meant is here any arbitrary 3 effervescent vitamin tablets available in Germany, because one single effervescent vitamin tablet contains 378.3 mg sodium/tablet on average. We specified the following sentence to clarify this part:
This amount of sodium is already contained in approximately 3 of the included effervescent vitamin tablets available in Germany (378.3 mg sodium/tablet on average).

30. Page 17, lines 12-15 (“9 million cardiovascular Events”): in China or worldwide? Please specify.

Author response:
This study refers to the Chinese population.
A modelling study from China showed that a reduction of 1,000 mg table salt/day could prevent approximately 9 million cardiovascular events in China by 2030, of which approximately 4 million are fatal.

31. Following discussion, putting the issue in the context, should be added: one sodium-rich dietary supplement tablet 1x/d for the whole year, over several years, can increase BP and the cardiovascular risk. However, 1-2 tablets a day of a sodium-rich cough & cold drug, taken for 3-4 days (typical duration of common cold symptoms requiring a tablet), are pretty unlikely to lead to such an increase, even if their sodium content is higher. Epidemiology and population risk reduction act over long periods of time. The difference between integrator/dietary supplements (which may have a lower sodium content but are usually taken throughout the year, or at least over one season) and common cold/cough OTC effervescent tablets taken for 3-4 days should be discussed.

Author response:
Indeed, thank you, this is an important aspect, that we have included in the discussion. We added the following part:
The intake of one sodium containing dietary supplement effervescent tablet per day for the whole year increases cardiovascular risk more likely than several pain/common cold effervescent tablets/day taken for 5-7 days only. A typical common cold lasts approximately 5-7 days, so the duration of the medical therapy is limited and the intake of OTC-effervescent tablets is rarely permanent. However, studies investigating the (temporary) intake of sodium-containing acetaminophen (paracetamol) effervescent tablets showed an increased risk for hospitalization for acute heart failure, cardiovascular disease and all-cause mortality (references: Perrin G, Arnoux A, Berdot S, et al. Association Between

Exposure to Effervescent Paracetamol and Hospitalization for Acute Heart Failure: A Case-Crossover Study. J Clin Pharmacol. 2022;62(7):883-890. doi:10.1002/jcph.2027 and Zeng C, Rosenberg L, Li X, et al. Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension. Eur Heart J 2022;43:1743–55. doi:10.1093/eurheartj/ehac059). The effect of permanent intake of sodium containing dietary supplement effervescent tablet could therefore be higher.

32. Another aspect to mention and to address in the Discussion section is that also some prescription medicines contain sodium. Of course, they may be life-saving and needed, and nobody would ever propose to avoid them because of their sodium content (among the several excipients any tablet contains). The key point, which should be made clear and stressed in the Discussion, is that the rationale for any drug intake (including dietary supplements and OTC drugs) should always be a risk/benefit balance. This study shows how important is that the same approach should apply also for OTC and dietary supplements. Indeed, this is probably the key message and conclusion of your study: dietary supplements are sometimes regarded as "sweets" / “candies”, but should be actually seen as drugs. The question should always be asked: is there a proven benefit? Is there any side effect (including sodium content)? What is the risk/benefit balance for this specific patient in this particular situation (or period of life)? Of course, this judgment may be difficult for the public (especially under the pressure of publicity and marketing initiatives). This discussion should be integrated in the manuscript.

Author response:
This is also an important comment and we agree with you, that this should be part of the discussion. Thank you.
The benefits of pharmacotherapy should always outweigh the risks/side effects. Most likely, the majority of the general population is unaware of the sodium content of effervescent tablets and dietary supplements are often regarded as “sweets”. Dietary supplements are considered “foods” by regulators and health benefits of many dietary supplements for healthy, asymptomatic and well-nourished adults have not yet been demonstrated in randomized clinical trials (references: Ronis MJJ, Pedersen KB, Watt J. Adverse Effects of Nutraceuticals and Dietary Supplements. Annu Rev Pharmacol Toxicol 2018; 58: 583–601. and Moyer MW. Nutrition: Vitamins on trial. Nature 2014; 510: 462–4.). Consequently, the harm might outweigh the benefit when people ingest several vitamin and electrolyte effervescent tablets daily, assuming they are doing something good for their health.

VERSION 2 – REVIEW

REVIEWER	Adedayo E. Ojo University of Abuja Teaching Hospital, Department of Internal Medicine
REVIEW RETURNED	24-Sep-2023

GENERAL COMMENTS	All the comments raised previously have been addressed.

REVIEWER	N. Nani National Defence University of Malaysia, Faculty of Medicine and Defence Health
REVIEW RETURNED	01-Oct-2023

GENERAL COMMENTS	The paper is well written. It gives insight on hidden sodium content in effervescent tablets. The limitations of the study have been appropriately addressed. The author has concluded this study with some suggestions which are relevant to the findings. It is worth discussing the comparison between effervescent formulation vs regular tablet in the risk/benefit justification.

REVIEWER	Sebastiano Lava University Children's Hospital Bern-University of Bern
REVIEW RETURNED	01-Oct-2023

GENERAL COMMENTS	The Authors satisfactorily addressed most of my previous comments (and I would like to thank them for the clarity of their point-by-point answers). The manuscript has improved. There are still, however, some opportunities for improvement, mostly aimed at further shortening the manuscript and at increasing its readability and appeal to the potential Readership. Page 5 of the pdf, lines 56-60 (“The median sodium content…” up to “… of the MRDSI).”): delete. Page 12, line 23 (“The median sodium content of a single effervescent tablet…”): do you mean the measured sodium content, right? If yes, please modify into “The median measured sodium content of a single effervescent tablet…”. Page 12, lines 48-54 (“The intake of eight tablets (maximum recommended daily dose) of Alka-Seltzer classic® (aspirin, Bayer) would lead to the ingestion of 3,560 mg sodium (figure 2), which encompasses 178% of the maximum recommended daily sodium intake.”): delete. Page 13, line 8/9 (“Supplement figure 3 summarizes the main results.”): delete. Page 13, lines 29-32 (“The sodium content was particularly high for pain/common cold tablets.”): delete. Page 13, line 32: “sodium, but as” -> “sodium, and as” Page 13, lines 50-53: “contained more sodium than declared” -> “contained more measured sodium than that declared” Page 14: “has been linked with serious” -> “has been linked to serious” Page 15, lines 36-41 (“Consequently, the consumption of effervescent tablets investigated herein may contribute to an increased cardiovascular risk”): delete. Page 15, line 55 (“Vitamin C 1000®…”) up to Page 16, line 15 (“…3,560mg sodium.”): delete. Page 16, lines 19-20: “(p=0.007). The majority of” -> “(p=0.007). Yet, the majority of” Page 18, lines 47-52 (“Randomized clinical trials are needed to examine the impact of effervescent tablets from grocery stores, discounters, drug stores, and pharmacies on cardiovascular risk.”): delete. Page 19, line 5/6: “are valide, is a limitation” -> “are valid, is a limitation” Page 19, lines 14-17: “contained high sodium, often unknown or neglected.” -> “contained high sodium.”

	Page 19, lines 17-19 (“Some products contain more sodium than others, although comparable in (active) ingredients.”): delete. Page 19, line 30/31: it may be beneficial to complete following sentence as suggested (or with other similar words): “… of hidden sodium. Finally, …” -> “… of hidden sodium, and to prefer non-effervescent alternatives containing the same active ingredients. Finally, …” Page 19, line 32/33: “requested” -> “prompted”

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

All the comments raised previously have been addressed.

Author response:

Thank you for your comments which improved the manuscript in a meaningful way.

Reviewer 2

The paper is well written. It gives insight on hidden sodium content in effervescent tablets. The limitations of the study have been appropriately addressed. The author has concluded this study with some suggestions which are relevant to the findings. It is worth discussing the comparison between effervescent formulation vs regular tablet in the risk/benefit justification.

Author response:

Thank you, an important aspect. We added the following marked part in the discussion section:

The benefits of pharmacotherapy should always outweigh the risks/side effects. Most likely, the majority of the general population is unaware of the sodium content of effervescent tablets and dietary supplements are often regarded as “sweets”. Dietary supplements are considered “foods” by regulators and health benefits of many dietary supplements for healthy, asymptomatic and well-nourished adults have not yet been demonstrated in randomized clinical trials.[27,28]. Consequently, the harm might outweigh the benefit when people ingest several vitamin and electrolyte effervescent tablets daily, assuming they are doing something good for their health. In addition, there is little reason to prescribe effervescent tablets because most active ingredients are also available as tablets not containing sodium.

[…]

Conclusion

[…]

Based on the study findings, patients at risk should be advised to limit effervescent tablets to prevent the ingestion of hidden sodium, and to select non-effervescent alternatives containing the same active ingredients.

Reviewer 3

The Authors satisfactorily addressed most of my previous comments (and I would like to thank them for the clarity of their point-by-point answers). The manuscript has improved.

There are still, however, some opportunities for improvement, mostly aimed at further shortening the manuscript and at increasing its readability and appeal to the potential Readership.

Author response:

Thank you for your detailed comments making the manuscript more precise. Your wording suggestions helped us to further improve the manuscript.

1. Page 5 of the pdf, lines 56-60 (“The median sodium content…” up to “… of the MRDSI).”): delete.

Author response:

We deleted this part of the abstract.

The median sodium content of recommended daily doses of the pain/common cold drugs was 2,776.5 mg (IQR: 1,299.8- 3,333.0 mg; 139% of the MRDSI).

2. Page 12, line 23 (“The median sodium content of a single effervescent tablet…”): do you mean the measured sodium content, right? If yes, please modify into “The median measured sodium content of a single effervescent tablet…”.

Author response:

No, the sodium content declared on the summary of product characteristics is listed here. This is evident from the sentence before (“The sodium content declared on the summary of product characteristics of the OTC drugs sold in Germany is listed in table 3.”). We changed the sentence:

The median reported sodium content of a single effervescent tablet was 157.0 mg (IQR: 98.9-417.3 mg; table 2 C).

3. Page 12, lines 48-54 (“The intake of eight tablets (maximum recommended daily dose) of Alka-Seltzer classic® (aspirin, Bayer) would lead to the ingestion of 3,560 mg sodium (figure 2), which encompasses 178% of the maximum recommended daily sodium intake.”): delete.

Author response:

We think it is important to illustrate the high sodium content of OTC drugs to the reader by providing an example. Furthermore, this sentence explains the meaning of figure 2 which is why we would like to keep as is.

4. Page 13, line 8/9 (“Supplement figure 3 summarizes the main results.”): delete.

Author response:

It is a requirement from the Journal, that every figure is listed and explained in the manuscript.

5. Page 13, lines 29-32 (“The sodium content was particularly high for pain/common cold tablets.”): delete.

Author response:

Done.

The sodium content was particularly high for pain/common cold tablets.

6. Page 13, line 32: “sodium, but as” -> “sodium, and as”

Author response:

Done.

The intake of the recommended daily dose of one OTC drug would lead to a median consumption of 384.0 mg sodium, and as high as 2,776.5 mg for pain/common cold drugs.

7. Page 13, lines 50-53: “contained more sodium than declared” -> “contained more measured sodium than that declared”.

Author response:

Done.

Of note, dietary supplement effervescent tablets available in Germany contained more measured sodium than that declared in those available in the United States of America.

8. Page 14: “has been linked with serious” -> “has been linked to serious”

Author response:

Done.

Dietary sodium intake has been linked to serious harmful effects, including BP elevation and all-cause death.

9. Page 15, lines 36-41 (“Consequently, the consumption of effervescent tablets investigated herein may contribute to an increased cardiovascular risk”): delete.

Author response:

Done.

Consequently, the consumption of effervescent tablets investigated herein may contribute to an increased cardiovascular risk.

10. Page 15, line 55 (“Vitamin C 1000®…”) up to Page 16, line 15 (“…3,560mg sodium.”): delete.

Author response:

We have shortened this part of the discussion:

The ancillary sodium intake through effervescent tablets is often neglected or unknown. Herein, the average sodium content of effervescent food supplements tablets in Germany was 283.9 mg/tablet, and the median sodium content of the pharmacy-only effervescent tablets was 157.0 mg/tablet. Consuming one of the included effervescent vitamin tablets or pain/common cold tablets corresponds to about one fifth (19%/23%) of the maximum recommended daily sodium intake. Six products (8.3%) contained more than 500 mg sodium/tablet. , Vitamin C 1000® (fit+Vital) and Vitamin C+Zink+Selen+Vitamin D3® (elkos Vivede) had the highest amount of sodium/tablet (564.7 mg and 541.1 mg) of the dietary supplements available in Germany. Vitamin products contained significantly more sodium than magnesium (p=0.004), calcium (p=0.006) and mineral (p=0.048) products; this might be due to different solubility properties. Of the OTC drugs, doxylamine 25 mg (Gittalun®, Hermes Arzneimittel) and aspirin 500 mg (Aspirin Migräne®, Bayer) had the highest amount of sodium/tablet (575 mg and 544 mg). With a maximum recommended daily dose of eight tablets/day, Alka-Seltzer classic® (324 mg aspirin, Bayer) would add a total of 3,560 mg sodium. The sodium content of the maximum daily dose of pain/common cold drugs was significantly higher than the sodium content of the maximum daily dose of calcium/vitamin D drugs ($p<0.0001$) and cough drugs ($p=0.007$). Yet, the majority of the general population and healthcare professionals alike are unaware of the high sodium content of effervescent tablets.

11. Page 16, lines 19-20: “(p=0.007). The majority of” -> “(p=0.007). Yet, the majority of”

Author response:

Done.

Yet, the majority of the general population and healthcare professionals alike are unaware of the high sodium content of effervescent tablets.

12. Page 18, lines 47-52 (“Randomized clinical trials are needed to examine the impact of effervescent tablets from grocery stores, discounters, drug stores, and pharmacies on cardiovascular risk.”): delete.

Author response:

Done.

Randomized clinical trials are needed to examine the impact of effervescent tablets from grocery stores, discounters, drug stores, and pharmacies on cardiovascular risk.

13. Page 19, line 5/6: “are valide, is a limitation” -> “are valid, is a limitation”

Author response:

Thank you.

Nevertheless, the assumption that the declared sodium content of dietary supplements available in the United States of America are valid, is a limitation.

14. Page 19, lines 14-17: “contained high sodium, often unknown or neglected.” -> “contained high sodium.”

Author response:

Done.

Dietary supplements and OTC effervescent tablets investigated herein contained high sodium, often unknown or neglected.

15. Page 19, lines 17-19 (“Some products contain more sodium than others, although comparable in (active) ingredients.”): delete.

Author response:

This is one of our main results, so we think this part is relevant for the conclusion.

16. Page 19, line 30/31: it may be beneficial to complete following sentence as suggested (or with other similar words): “… of hidden sodium. Finally, …” -> “… of hidden sodium, and to prefer non-effervescent alternatives containing the same active ingredients. Finally, …”

Author response:

Thank you, a good wording suggestion.

Based on the study findings, patients at risk should be advised to limit effervescent tablets to prevent the ingestion of hidden sodium, and to select non-effervescent alternatives containing the same active ingredients.

17. Page 19, line 32/33: “requested” -> “prompted”

Author response:

Done.

Finally, we suggest that manufacturers should be prompted to reduce sodium in their effervescent formulations.