PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluation of exposure to effervescent drugs in a large health check-up population in France: A cross-sectional study
AUTHORS	Perrin, Germain; Berdot, Sarah; Thomas, Frédérique; Pannier, Bruno; Danchin, Nicolas; Durieux, Pierre; Sabatier, Brigitte

VERSION 1 – REVIEW

REVIEWER	Maryse Lapeyre-Mestre Université de Toulouse, France
REVIEW RETURNED	13-Mar-2018

GENERAL COMMENTS	This is an interesting study dealing with the problem of sodium intake through the use of drugs presented as effervescent tablets. The study is original itself by its topic (an investigation of ET patterns of use in a non-morbid population, close to the general population) and the way to investigate it. Actually, people attending this kind of medical center are not people seeking care, but a mix of deprived population (they can have access to a complete health checkup for free) and healthy people. This study population is in the same time a strength and a limitation of the study, and some of the results could discussed in depth regarding this dual population. I suggest to avoid the term “primary care population”, since this is a healthy population (page 4, line 56), more representative of the general population (a comparison of self-medication patterns in studies performed in healthy workers could be interesting). Table 1 gives a picture of the repartition of ET use and social deprivation, surprisingly people with social deprivation are more likely to use ET frequently (even if it is not statistically significant). It raises the question of health care access for people with low income. One other interesting point is the lack of knowledge of participating subjects (and also of some health professionals) about salt intake through medications, as discussed by the authors (page 13, line 22-34). This is not a direct result of this study, but it seems important to underline that 10% of the WHO maximum sodium intake is provided only through medications (self-medication or prescription only drugs). This intake does not take in account other sources of sodium in meals and water. Did the authors investigate with these data, other sources of sodium intake? My major concern about this analysis is the problem of polymedication, which is not included as confounding factor. The risk of iatrogenic events is directly proportional with the number of different drugs taken concomitantly, and in this way, we can expect an increasing iatrogenic risk with self-medication (by adding another drug and by increasing the risk of misuse, for example intake of high amount of sodium for a patient treated for hypertension). It would be interesting in this study to adjust on a potentially

	important confounding variable, i.e. the number of different drugs used by the patients, rather than on comorbidities which are very low in this population. Minor points : Abstract (page 2 line 16) : Because the design is a cross sectional study, by definition this is not a prospective study. This is a cross-sectional study with a prospective data collection Page 5 , line 7, this is a sample, not a cohort Page 9, line 22 : there is a misunderstanding, in table 1, place of birth is divided in France, French overseas, and other, and in the text, “were more frequently from Europe”. Please check and correct

REVIEWER	Anne Elise Eggen Department of Community Medicine, UiT The Arctic University of Norway, Norway
REVIEW RETURNED	23-Mar-2018

GENERAL COMMENTS	Abstract This is a cross-sectional study, where information about the exposure is collected through self-report of past use of drugs. The other variables are collected at attendance. Why do the authors call this study prospective? In results they state that overweight is measured as > 25 kg.m-2. The traditional way of defining overweight is ≥ 25 kg/m2. Strength and limitations of the study The authors state: Due to the single center design, we must be cautious in generalizing these results. It may be a larger problem that this is a very selected group of patients. Introduction The authors refer to a literature where it seems like all agree that high intake of salt leads to high blood pressure. However, the evidence for the effect from salt-reduction on cardiovascular disease seems more unclear. WHO has, however, made recommendations about restriction on the daily intake of salt or sodium. The authors’ project focuses on the contribution of pharmaceutical preparation to the daily salt or sodium intake. I have a problem understanding the order of magnitude the contribution from two effervescent tablets (ET) of aspirin compared to the contribution from the food intake. If I had a better understanding of this, it had been easier to understand why this is an important health issue. Methods The participants in the study was recruited from a medical center subsidized by the French National Healthcare System and proposes all insured and retired individuals (and their families), living in Paris and its suburbs, a free medical examination every five years. Impoverished individuals are eligible for a free medical examination every year. This seems like a rather selected population that can influence the prevalence estimate, as well as the factors associated with ET use. The authors state “During the educational session on salt consumption, the subject completed a specific questionnaire with the pharmacist.” Does this mean that all participants were assisted when they filled in the questionnaire, and the pharmacist could see everything a participant filled in? This questionnaire assessed the consumption of ETs, through medical prescription and self-medication. Was prescriptions from dentists included? Self-medication was defined as the use of any drug without a medical prescription (this included drugs bought in a community pharmacy or directly taken from the medical cabinet). What is the

	definition of medication? Is it every remedy a person take for health reasons? Once identified, drugs were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System. There should be a reference to the WHO center and the classification system.. The frequency of exposure was classified into: 1. “At least 1 ET once a month”, 2. “At least once a week”, 3.“two or three times per week”, 4.“four to six times per week” and 5.“once a day or more”. Subjects were defined as A.unexposed if they did not use any ETs during the last 30 days preceding the medical check-up, B. occasionally exposed if they reported the use of ETs no more than once a week (i.e.1+2), and C. frequently exposed if they reported the use of ETs at least twice a week (3+4+5?). Had the participants in the collapsed groups used the same amount of tablets in all the weeks of the 30 days time window, i.e. they had used the same amount of ET every week of the 30 days period? The authors use the term morphometric parameters. This is new to me. Is this the same as anthropometric? Page 6. The examination at attendance was very extensive, very many biological measurement and batteries of questions. For example large depression score, stress and socioeconomic status (SES). SES alone included 42 questions. However, salt intake was only measured through self-report, a food frequency questionnaire Exsel) , and no biological measurement of salt intake as 24-h-urin sampling. It is difficult to see the connection between all the information gathered and the aim of the project. Has the Exsel questionnaire been validated? A huge amount of variables are collected, few showed to be significant. I would like to see what kind of model the authors had made about the associations between the variables before they started the analyses, e.g. what did they think about the association between socio-economic position and the use of ET? Ethics What do the authors mean when they write the following: “data was anonymously collected during voluntary health check-ups”? How could the variables be anonymously collected when a pharmacist, a physician or research technicians followed the health examination and collection process closely? Results I do not understand the sentence Exposure through self-medication was associated with a smaller estimated amount of drug-associated sodium intake relative to that of prescribed drugs (2.2 +/- 2.7g? vs 11.3 +/- 14.5g, p < 2 x 10-16). The meaning of this is probably that those who use effervescent Rx medication use them on a daily basis? Figure 2. The text should define the relevant products in the group A and N, and they should use the relevant ATC-codes. Now it is open to speculation what is in the main group A and N. What is the atc code for multivitamins, boldine and betaine citrate? Are these ingredients defined as drugs in France? B) by molecule? I would say by active ingredients, but “the vitamins” is a huge group. Is it multivitamin tablets and Vitamin C who are the relevant preparations? Figure 3. What does this plot show me? Is it one dot per person? It looks like almost all of the 280 participants had used ET that contributed less than 20 per cent of the recommended level of the WHO threshold. The few dots between 20 and 100, what ET are they using? The authors write: ”Nevertheless, a non-negligible proportion of subjects were exposed to higher quantities of sodium, above the WHO threshold of 20%, resulting in an increase of global

	sodium intake." Above the WHO threshold of 20%?, is that a specific threshold of concern because the authors think this "high" ET use gives a significant contribution to the salt intake? Table 1 The authors write: Frequently exposed subjects trended towards a higher BMI, were more frequently from Europe (excluding France) or Overseas France, had a higher level of stress, were more depressed, and had lower perceived health quality than unexposed subjects. No biological parameter significantly differed between exposure groups, although there was a trend towards higher creatininemia in the exposed group relative to the unexposed group (reflected by a significantly higher proportion of subjects with EGFR < 90 mL/min in the exposed than unexposed group, p = 0.02). Smoking status, regular alcohol consumption, regular physical activity, and regular soda consumption were not significantly associated with the consumption of ETs. It is difficult to figure out what kind of model the authors have had in their mind, how these variables are associated. How is the correlation between SES score and Overseas France place of birth? If depression is a factor, is that because there are several antidepressants as ET in France? Should we expect higher blood pressure among those frequently exposed on ET? At the bottom of the table I find the following: °p < 0.033, *p < 0.017, **p < 0.003, ***p < 0.0003 (Bonferroni correction). What is the reason for this line? Figure 4 What do the red dots mean? What's the label on the y-axis? What is the big picture in these analyses? Discussion with 7.3% of subjects declaring the consumption of at least two or three ETs per week in the last 30 days. Do they have this consumption every week in the 30-days-interval? Self-medication was the main source of exposure in this population, in which subjects exhibited a low level of comorbidity and cardiovascular risk, with vitamin therapy as the principle class involved (ahead of analgesics). Is use of multivitamins a therapy for specific diagnoses? This study was performed from April to June (2017). Do this mean extensive examination of 14.6 fasting participants every day for 90 workdays? Finally, the prevalence of comorbidities, usually associated with the choice of effervescent formulations (i.e. neurodegenerative disorders, stroke recovery, dysphagia in elderly subjects) was very low, leading to a possible underestimation of the true prevalence in a more general outpatient setting population. Do the patients mentioned here go to another clinic? In multivariate analysis, male gender, origin of the subject, and a high depression score were the only independent predictive factors for exposure to ETs. It is possible to explain this more in depth? Very many variables have been included, and the analyses end up with that being male and born in the region of overseas France are the only significant associations with ET use? What was the model? Surprisingly, social deprivation was not a protective factor against exposure to ETs, as exposure was mostly by self-medication. This can also be explained by the definition of self-medication used: impoverished individuals can benefit from reimbursement of their prescribed medications, making ETs widely available via their medicine cabinet throughout the year. What is the connection between use of ET and social deprivation? Why are the authors surprised? Has this something to do with the structure of the

	governmental reimbursement system for drugs in France? As a last remark: It is difficult to understand the order of magnitude, i.e. how important health issue is the use of ET, and second what can we learn from the pattern of associated factors found for ET use? Third, what is the association of ET use and high blood pressure? There are some significant p-values in Online resource 1, but I cannot find comments on these findings in the text. I hope my comments are helpful.

VERSION 1 – AUTHOR RESPONSE

1. Reply to the Editor

For better clarity we provide a point by point discussion.

1.1 Please revise the title of your manuscript to include the country.

Reply and changes made:
Title of the manuscript has been amended following this comment.

1.2 BMJ Open now requires authors of all submissions to the journal to include a Patient and Public Involvement statement.

Reply and changes made:
A paragraph entitled "Patient and public involvement" has been added as a sub-heading at the end of the "Methods" section.

2. Reply to Reviewer #1

We would like to thank Maryse Lapeyre-Mestre for her interest in our study and for her relevant and expert reviewing.

2.1 This study population is in the same time a strength and a limitation of the study, and some of the results could be discussed in depth regarding this dual population.

Reply:
We acknowledge that social deprivation is associated with higher difficulties in accessing the health care circuits, particularly those poorly covered by social security services (typically in France: dentistry, specialist doctors etc.). Predicting whether social deprivation should be associated with a lower rate of self-medication, and thus with a lower exposure to ETs (given the important variety of ETs available without medical prescription in France), seems tricky. Indeed, a subject can self-medicate with ETs that have been reimbursed months ago for any medical reasons which led to a medical prescription. Our results did not find any differences for exposure to ETs regarding the score of social deprivation.

Changes made:
This limitation has been added in the “Strengths and limitations” section and discussed in the “Discussion” section.

2.2 I suggest to avoid the term "primary care population", since this is a healthy population, more representative of the general population.

Reply:
We agree with this comment. However, we do not think that our study population is a representative sample of the general population, since it was characterized, for example, by a small proportion of women (39.7%), and by a low prevalence of diabetes mellitus (as shown in Online resource 1).

Changes made:
We corrected the manuscript by replacing all occurrences of "primary care population" by "health check-up population", in order not to mislead the readers.

2.3 A comparison of self-medication patterns in studies performed in healthy workers could be interesting.

Reply:
We do agree that this kind of study is of great interest in order to discuss the results presented in this manuscript. Our reference list includes a review investigating patterns associated with self-medication in France (Raynaud et al., reference 19). This analysis investigated the influence of occupational status in the recourse to self-medication and showed that unemployment was negatively associated with self-medication. This result led us to hypothesize that social deprivation (used in our study as a proxy of the occupational status) should be taken into account in our analysis of the factor associated with exposure to ETs, since these formulations are widely available over-the-counter in France.

Changes made:
For more clarity in the reading of results of the analysis, we added a sub-heading "Hypothesis" in the "Methods" section, where we clearly stated the underlying hypothesis associated with the including of some specific variables in the analysis.

2.4 It raises the question of health care access for people with low income.

Reply:
This point has been developed in 2.1.

2.5 Did the authors investigate with these data, other sources of sodium intake?

Reply:
Indeed, in this work, we decided to investigate dietary sodium intake, beside drug-associated sodium intake (as shown in Table 2 & discussion), in order to investigate a possible correlation between high dietary sodium intake and preference for ETs. Such a correlation could suggest a craving for salt associated with effervescent formulations. In this context, we also investigated (see Figure 4) whether the taste of ETs (generally characterized as “salty”) was a factor associated with preference for these formulations. Our results showed that frequently exposed subjects had a higher preference for ETs based on their taste, compared to occasionally exposed subjects.

2.6 My major concern about this analysis is the problem of polymedication, which is not included as confounding factor. The risk of iatrogenic events is directly proportional with the number of different drugs taken concomitantly.

Reply:
We do agree with the role of polymedication (defined as the administration of an excessive number of drugs by the WHO in 2004 in its Glossary of terms for Community Health care and services for older persons; or with the use of 5 drugs or more, according to Gnjidic et al. 2012) in increasing the risk of iatrogenic events, especially in elderly population. Nevertheless, the aim of our analysis was not to

assess directly the clinical consequences associated with exposure to ET, but was to perform a drug utilization study, with an investigation of patterns associated with this utilization.

Our logistic regression model was:
Y: exposure to ETs in the last 30 days, Yes/No
Xi: covariables of interest potentially associated with exposure.

Because cross-sectional design is not suited for causal inference, we are currently completing this work with a study in which we will investigate the potential iatrogenic consequences associated with exposure to ETs in a high-risk population. This analysis will include polymedication and Charlson comorbidity score as confounding factors.

Changes made:
Because the information concerning the number of drugs used by each participant was available in our database, we added this information in Table 1. We used a threshold of 5 drugs or more to define polymedication. Since there were no differences between exposure groups for this variable (with p-values > 0.2), we did not include this variable in our multivariate models, as prespecified in the "Methods" section.

2.7 This is not a prospective study. This is a cross-sectional study with a prospective data collection.

Reply and changes made:
The abstract has been amended in order to clarify our misleading formulation.

2.8 This is a sample, not a cohort.

Reply and changes made:
In order to clarify the sentence, we modify "study population" by "study sample".

2.9 There is a misunderstanding in table 1, place of birth is divided in France, French overseas, and other, and in the text, "were more frequently from Europe". Please check and correct.

Reply:
The full description of the different places of birth is given in Online resource 1. We do agree that this information is missing while reading the main document, leading to a lack of clarity.

Changes made:
We added the detail of the different places of birth in Table 1.

3. Reply to Reviewer #2

We would like to thank Anne Elise Eggen for her extensive review and for her helpful comments that clearly improve the quality and the readibility of the manuscript.

3.1 Why do the authors call this study prospective?

Reply:
Indeed, our sentence was misleading. It was a cross-sectional study with a prospective data collection.

Changes made:

Abstract was amended to correct this sentence.

3.2 The traditional way of defining overweight is ≥ 25 mg/m².

Reply:
Thank you for detecting this typing error. We checked our script in R, and we did use ">= 25" while generating the "overweight" variable.

Changes made:
Abstract was amended to correct this error.

3.3 It may be a larger problem that this is a very selected group of patients.

Reply:
We totally agree with this comment, that has been developed in the “Discussion” section.

Changes made:
We amended the “Strengths and limitations” section in order to take into account this comment.

3.4 However, the evidence for the effect from salt-reduction on cardiovascular disease seems more unclear.

Reply:
Indeed, this point is a major pitfall while addressing the problem of how to build a salt reduction policy at a population level. Additionally, some authors suggested that drastic low salt intake could be associated with excess mortality, with J or U shaped curved between cardiovascular mortality and level of salt intake (O’Donnell et al., NEJM 2012). However, in the present work, we were not investigating a salt-reduction strategy, but rather a potential source of excessive sodium intake, that can worsen the dietary sodium intake (we are not focusing on the controversy part of the J or U shaped curved).

3.5 I have a problem understanding the order of magnitude the contribution from two ET of aspirin compared to the contribution from the food intake. If I had a better understanding of this, it had been easier to understand why this is an important health issue.

Reply:
Because some studies suggested that regular exposure to ETs could be associated with cardiovascular events, and because these formulations have very large sale volumes in France (effervescent paracetamol was in the top 3 of optional medical prescription drugs in 2013), we decided to investigate which type of subjects were more frequently exposed to ETs. This is an important information since several alternatives to ETs are available (over-the-counter or with a medical prescribing, such as orodispersible formulations).
We do agree that a subject exposed to 2 ETs of aspirin in a 30-day period may not increase significantly his cardiovascular risk, but this could indicate that, if this subject declares a chronic disease in the future (such as chronic osteoarticular pain), he may be more likely to use an effervescent formulation (this prevalence in a relatively healthy population is the reflect of the pool of potential users of ETs).
A recent clinical trial, published in March 2018, demonstrated, with a crossover, randomized design, that exposure to 3g effervescent paracetamol during a 3 weeks period in hypertensive subjects was associated with a significant increase in 24-h systolic BP measurement (3.99 mmHg in the intention-

to-treat analysis, and 5.04 in the per protocol analysis), compared to a 3 weeks exposure to non-effervescent paracetamol.
Altogether, this information made the knowledge of the patterns associated with exposure to ETs an important information for healthcare professionals: is hypertension or history of cardiovascular diseases protective factors against utilization of ETs (as expected)? What is the main source of exposure?

Changes made:
We added the reference of the crossover trial of Benitez-Camps et al. The “Discussion” section has been amended accordingly. Furthermore, we removed from the “Discussion” section the paragraph introducing the protocol paper of Benitez-Camps published in 2015, since the results of the trial was published in March, 2018.
3.6 This seems like a rather selected population that can influence the prevalence estimate, as well as the factors associated with ET use.

Reply and changes made:
This limitation has been clearly stated in the “Strengths and limitations” section (see 3.3), and in the “Discussion” section.

3.7 Does this mean that all participants were assisted when they filled in the questionnaire, and the pharmacist could see everything a participant filled in?

Reply:
This was a self-administered questionnaire. Pharmacist was eventually requested if the subject had difficulties to understand specific questions but did not interfered in the content of the responses. Only after they completed the questionnaire, all participants were proposed an educational session on salt consumption, including advices about utilization of ET. Participants were not allowed to modify their responses following this educational session.

Changes made:
We modified the sentence in the “Methods” section in order not to mislead readers. Additionally, we clarified this point in the “Patient and public involvement” section.

3.8 Was prescriptions from dentists included?

Reply:
Indeed, we included prescriptions from all authorized healthcare professional categories, including dentists.

Changes made:
Methods, section b. has been clarified accordingly.

3.9 What is the definition of medication? Is it every remedy a person take for health reasons?

Reply:
We used the definition of the “medicinal product” given by article 1 of the Council Directive 65/65/EEC, i.e. “any substance or combination of substances presented for treating or preventing disease in human beings or animals”.

Changes made:
We added the reference to the European Council Directive in the “Methods” section.

3.10 There should be a reference to the WHO center and the classification system.

Reply and changes made:
The reference to the WHO classification system has been added in the “Methods” section.

3.11 Had the participants in the collapsed groups used the same amount of tablets in all the week of the 30 days time window, i.e. they had used the same amount of ET every week of the 30 days period?

Reply:
This was a semi-quantitative estimation, using pre-specified categories of exposure as described in the “Methods” section. Participants identified the category of exposure that fitted at best their ET utilization in the last 30 days. They were then invited to refine the exposure estimate by precising the number of ET per administration. This resulted in a smoothed estimation of the daily exposure. However, this semi-quantitative estimation allowed the discrimination between occasional users and frequent users.

Changes made:
In the “Discussion” section, we clearly stated the semi-quantitative and smoothed nature of the estimate of exposure to ETs.

3.12 Is this the same as anthropometric?

Reply and changes made:
We rewrite the sentence using “anthropometric”.

3.13 It is difficult to see the connection between all the information gathered and the aim of the project […] I would like to see what kind of model the authors had made about the association between the variables before they started the analysis, e.g. what did they think about the association between socio-economic position and the use of ET?

Reply:
All the variables included in Table 1 and in the statistical models aimed: (i) the provide a basic description of the population (sex, age etc.), and (ii) to test hypothesis we made at the step of designing the study. For example, as we discussed in 2.3, we found in the French literature that occupational status was negatively associated with the recourse to self-medication. Given the wild availability of ET over-the-counter, we speculated that socio-economic position could be a protective factor against exposure to ETs.

Changes made:
As mentioned in 2.3, we added a section describing the underlying hypothesis we prespecified before starting the study, and the variables associated with each hypothesis. We hope that this make the aim of the project easier to capture.

3.14 Has the Exsel questionnaire been validated?

Reply:
Indeed, the Exsel questionnaire has been validated against 24-hour urinary sodium collection (considered as a gold standard for estimation of dietary sodium intake) in a French hypertensive

population (Girerd et al. 2015, see reference 25). This food frequency questionnaire includes items concerning consumption of high salt food (bread, cheese, charcuterie, processed broth or pilaf, industrialized food). Excess dietary sodium intake was defined with ≥ 200 mmol/d. The ROC curve analysis showed that a score of 5 or more has the best Youden index with a sensitivity of 0.63, specificity of 0.95, NPV of 0.92, PPV of 0.75.

3.15 What do the authors mean when they write the following: “data was anonymously collected during voluntary health check-ups”?

Reply:
At the step of administrative registration, each subject is assigned a unique IPC number, that allows the linkage between biological results, data collected by physician and data collected for specific research protocols. This anonymization process has been approved by the French ethic authority (Commission Nationale de l’Informatique et des Libertés, CNIL).

Changes made:
The “Ethic” section has been clarified accordingly.

3.16 I do not understand the sentence “Exposure through self-medication was associated with a smaller estimated amount of drug-associated sodium intake relative to that of prescribed drugs (2.2 +/- 2.7g vs 11.3 +/- 14.5g, p < 2 x 10-16”.

Reply:
With this sentence, we meant that according to the semi-quantitative estimation, patients who used ET through self-medication had an estimated drug associated sodium intake of 2.2 +/- 2,7g in the last 30 days, whereas those who used ET through medical prescribing had an estimated drug associated sodium intake of 11.3 +/- 14.5g (p < 2.10-16).

Changes made:
We rewrite this sentence in order to make it clearer for readers.

3.17 The text should define the relevant products in the A and N, and they should use the relevant ATC-codes.

Reply and changes made:
As requested, we added the relevant products and relevant ATC-codes in the text.

3.18 What is the ATC code for multivitamins, boldine and betaine citrate? Are these ingredients defined as drugs in France?

Reply:
According to the ATC classification, the following codes were used to encode the drugs:
- Multivitamins: A11A (multivitamins, combinations); A11B (multivitamins, plain), A11G (ascorbic acid (vitamin C), including combinations), A11J (other vitamin products, combinations).
- Boldine: A05C (Drugs for bile therapy and lipotropics in combination).
- Betaine citate: A16AA06 (betaine).

Indeed, these ingredients are defined as drugs in France, according to the regulatory definition given by the Code de la Santé Publique (L511-1), similar to the definition given by Article 1 of the Council Directive 65/65/EEC, i.e. “any substance or combination of substances presented for treating or preventing disease in human beings or animals”.

Changes made:
Reference to the article 1 of the Council Directive 65/65/EEC has been added in the “Methods” section.

3.19 I would say by active ingredients.

Reply and changes made:
The sentence has been amended using “active ingredients”.

3.20 Is it multivitamin tablets and Vitamin C who are the relevant preparations?

Reply:
We do agree that vitamin is a huge group. As it has been suggested, multivitamins (with minerals, ATC code A11A) and Vitamin C alone (ATC code A11GA01) were the two preparations found in our study. Among the 60 preparations with vitamins declared by participants, 23 were Vitamin C alone (38%) and 37 were multivitamins with minerals (62%).

Changes made:
The detail of the relevant preparations has been added in the “Results” section.

3.21 What does this plot show me? Is it one dot per person?

Reply:
Indeed, Figure 3 is a violin plot where 1 exposed subject has been represented with 1 dot. In Y-axis, the different levels of Na intake (in % of the WHO recommended daily intake), has been added. The aim of this Figure is to give an order of magnitude of the importance of drug-associated sodium intake, relative to dietary sodium intake. Actually, in the present sample, reflecting a relatively healthy population, Figure 3 shows that for most exposed subjects, the drug associated sodium intake does not appear to be a big issue, except for a non-negligible proportion of subjects, for who drug associated sodium intake was higher than 20% of the recommendations.

Changes made:
We clarified the caption of Figure 3, and we rewrite the “Results” section accordingly.

3.22 The few dotes between 20 and 100, what ET are they using?

Reply:
They were 10 participants (#1% of the sample) who declared a drug associated sodium intake that was estimated between 20 and 100% of the WHO threshold. From these 10 participants, two were hypertensive. Nine of them declared utilization of one type of ET in the last 30 days, although one participant declared the utilization of 3 different ETs.

In detail, the ATC codes were:
- N02BE01 (paracetamol): 6/12
- N02BA (aspirin): 3/12
- A11GA01 (vitamin C alone): 2/12
- C05C (capillary stabilizing agents): 1/12.

Changes made:
This supplemental information has been added in the “Results” section.

3.23 “Above the WHO threshold of 20%”. Is that a specific threshold of concern because the authors think this “high” ET use gives a significant contribution to the salt intake?

Reply:
This specific threshold has been proposed by the European Medicines Agency (EMA). Indeed, the EMA published in 2017 a revision of its guideline “Excipients in the label and package leaflet of medicinal products for human use”. They stated that: “17 mmol (391 mg) is approximately 20% of the WHO adult recommended maximum daily dietary intake of 2 g sodium and is considered to represent ‘high’ sodium”.

Changes made:
The reference to the EMA guideline has been updated in the reference list, and we clearly stated the choice of this threshold in our “Methods” section.

3.24 It is difficult to figure out what kind of model the authors have had in their mind, how these variables are associated. How is the correlation between SES score and Overseas France place of birth? If depression is a factor, is that because there are several antidepressants as ET in France?

Reply:
As mentioned in 3.13, we described the underlying hypothesis associated with the inclusion of all covariables in our analysis. For the diagnosis of depression, no antidepressant is formulated as effervescent tablets in France. Because ET are sometime described as “pleasurable” or “restful” formulations (this subjective allegation being partially supported by the results given in Figure 4, panel d), we decided to investigate subjective variables associated with psychosomatic disorders.

3.25 Should we expect higher blood pressure among those frequently exposed on ET?

Reply:
This is clearly the cornerstone hypothesis of this project. This was initially based on low evidence literature, such as an uncontrolled-before after study published by Ubeda et al. in 2009 in Pharmacoepidemiology and Drug Safety, in which discontinuation of chronic treatment with effervescent paracetamol in hypertensive subjects with osteoarticular pain was associated with a strong and significant decrease in SBP. As mentioned in the “Introduction” section, George et al. published in 2013 a nested case-control study in which ~ 61000 cases has been compared to ~ 61000 controls. Authors found a strong association between diagnostic of hypertension and exposure to high-sodium containing drugs (OR: 7.18, 6.74 to 7.65). This low evidence literature has been strengthened in 2018 with the publication of a clinical trial, with a randomized crossover design, who found that exposure to effervescent paracetamol in a daily basis during 3 weeks was associated with an increased BP, measured with 24h-BP recording.

In this analysis, we found that office BP measurement was significantly higher in the frequently exposed group, relative to unexposed group, after adjustment for age and sex (result shown in Online resource 1). This result should be interpreted very cautiously because of the cross-sectional design of the study.

Changes made:
We added clearly this hypothesis in the “Introduction” section with the reference of the randomized crossover trial of Benitez-Camps et al., and we put the results of SBP and DBP from Online Resource to Table 1, with discussion of these results in the text.

3.26 At the bottom of Table 1, I find the following: °p < 0.033, *p < 0.017 […]. What is the reason for this line?

Reply:
Since we performed multiple comparisons involving 3 groups, the threshold p-value of 0.017 was considered for statistical significance, according to the applied Bonferroni correction.
Changes made:
We added this explanation in the “Methods” section and removed the corresponding line at the end of Table 1.
3.27 What do the red dots mean? What’s the label on the Y-axis? What is the big picture in these analyses?
Reply:
In the boxplot representation, dots outside the box (the red dots in Figure 4) represent the “outliers”, i.e. the observations that are not comprised in the interval between Q1 – 1.5*IQR and Q3 + 1.5 IQR (Q1: 25th percentile, Q3: 75th percentile, and IQR: inter-quartile range).
The label on the Y-axis is the Likert value for each subjective factor investigated.
This analysis aimed to explore potential subjective factors associated with the preference for effervescent formulation, especially when a sodium-free alternative is available. Indeed, even if a subject had swallowing difficulties, or an acute pain that need a fast relief, standard formulation such as orodispersible drugs can be used without the potential issue of exposure to important amount of sodium. Identifying such factors is important for healthcare professionals in order to adapt their recommendations and/or prescriptions.
Changes made:
We added the meaning of red dots in the caption of Figure 4. We added the label of Y-axis.
3.28 Do they have this consumption every week in the 30-days interval?
Reply:
This point has been developed in 3.11.
3.29 Is use of multivitamins a therapy for specific diagnoses?
Reply:
We did not analyze in the present study the medical indication of each drugs, but multivitamins are generally associated with preventive purposes (to our knowledge, there is no specific medical diagnoses associated with the use of multivitamins identified in our study, except scurvy for vitamin C but the prevalence of scurvy is dramatically low in France).
3.30 Do this mean extensive examination of 14.6 fasting participants every day for 90 workdays?
Reply:
The time required for a participant to complete the self-questionnaire and to see the pharmacist for the educational session was around 5 to 15 minutes. The recruitment was realized in 40 workdays between April to June 2017 (see the detail in Figure below). This corresponded to an average 26 participants evaluated per day.

3.31 Do the patients mentioned here go to another clinic?
Reply:
IPC center aims to provide preventive examinations to participants. Subjects with serious medical conditions (with history of stroke, of neurodegenerative disorders, with dysphagia associated with cancer treatment etc.) are unlikely to benefit from such preventive examinations. Rather, they are referred to more classical healthcare circuits.
Changes made:
The “Discussion” has been clarified accordingly.

3.32 “In multivariate analysis, male gender, origin of the subject and high depression score were the only independent predictive factors for exposure to ETs”. Is it possible to explain this more in depth? Very many variables have been included and the analysis end up with that being male and born in the region of oversea France are the only significant association with ET use? What was the model?

Reply:

As explain in 2.3 and 3.13, we added a description of our pre-specified hypothesis and corresponding covariables studied to test these hypotheses.

3.33 What is the connection between use of ET and social deprivation? Why are the authors surprised? Has this something to do with the structure of governmental reimbursement system for drugs in France?

Reply:
We speculated that, given the existence of a large number of effervescent formulations available over the counter in France (such drugs can not be reimbursed by the French governmental system for health, typically vitamins), social deprivation (interpreted as a proxy for socioeconomic status) should be associated with a lower access to such drugs. We did not observe any negative association between these two variables.

Changes made:
We hope that the “Hypothesis” section permitted a better understanding of this sentence.

3.34 It is difficult to understand the order of magnitude, i.e. how important health issue is the use of ET.

Reply:
We do believe that this crucial point has been clarified with the responses given in 3.5 and 3.25.

3.35 What can we learn from the patterns of associated factors found for ET use?

Reply:
In the field of preventive cardiology, these patterns are of interest since some of them are typical cardiovascular risk factors (i.e. male gender or being overweight). Some of them are emerging cardiovascular risk factor (i.e. depression). Additionally, being from Oversea France is associated with a high probability of being black (most of the subject were from French West Indies). This point is of interest since these populations have dietary habits associated with high salt consumption, and since being black (or Asian) is a recognized factor associated with salt-sensitive blood pressure.

From the viewpoint of a healthcare professional, we can learn even more from the patterns of factors that were not associated with ET use: particularly, all medical conditions associated with low salt requirement, like hypertension or treatment with diuretics (given the low prevalence for other comorbidities, like heart failure or history of stroke, it is not possible to draw conclusion). The information about the risk associated with utilization of ET by patients with low salt requirement is clearly indicated, and in a readily available fashion, in the leaflet of the product. This is not a direct result of our study, but it suggests a lake of awareness of both patients and practitioner about this specific and avoidable pitfall.

Changes made:
The discussion has been clarified according to the different points discussed above.

3.36 What is the association between ET use and high blood pressure. There are some significant p-values in Online resource 1, but I cannot find comments on these findings in the text.

Reply and changes made:
As discussed in 3.25, we added the results for SBP and DBP from Online resource 1 to Table 1 and we discussed these results in the “Discussion” section.

VERSION 2 – REVIEW

REVIEWER	Maryse Lapeyre-Mestre Université de Toulouse-3, UMR UPS-Inserm 1027, France
REVIEW RETURNED	09-May-2018

GENERAL COMMENTS	I would like to thank the authors for this revised version and their efforts to improve their manuscript The adding of their research hypothesis clarifies their approach for my reading. I do not have any other comments. Minor detail: Is the Exsel score a registered tool? According to the intellectual property's principle, I believe that the original reference for Exsel validation (or first steps of presentation, i.e. ref 25) should be repeated in the discussion (page 16, line 7).

VERSION 2 – AUTHOR RESPONSE

Reply to Reviewer #1

Minor detail: Is the Exsel score a registered tool? According to the intellectual property's principle, I believe that the original reference for Exsel validation (or first steps of presentation, i.e. ref 25) should be repeated in the discussion (page 16, line 7).

Reply and change made:

Indeed, the Exsel score is a registered tool (see reference 25). This tool is used for example by the French Committee for the Fight against High Blood Pressure (CFLHTA: Comité Français de Lutte contre l'Hypertension Artérielle), to screen for excessive sodium intake in hypertensive subjects (available in: http://www.comitehta.org/testez-vous/consommez-vous-du-sel-en-exces-test-exsel/; last access 24 of May 2018).

The original reference for Exsel validation has been repeated in the discussion, page 16, line 7.