

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Consumption of analgesics before a marathon increases the incidence of cardiovascular, gastrointestinal, and renal problems in a dose-dependent manner
<b>AUTHORS</b>	Brune, Kay; Kuester, Michael; Renner, Bertold; Opiel, Pascal; Niederweis, Ursula

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Tamara Hew-Butler DPM, PhD, FACSM Assistant Professor, Exercise Science Oakland University, Rochester, MI, USA  I have no conflicts of interest.
<b>REVIEW RETURNED</b>	16-Oct-2012

<b>THE STUDY</b>	I don't see any supplemental documents.
<b>RESULTS &amp; CONCLUSIONS</b>	The Tables are very cumbersome and confusing.
<b>GENERAL COMMENTS</b>	<p><b>General Comments:</b></p> <p>This is an interesting report on the effect of analgesic medications on the incidence of adverse events (AE) following a marathon/half marathon event. The combination of: a large (~4000) cohort; targeted analyses specific to gastrointestinal, renal and cardiovascular events; and ~50/50 split between runners who did and did not ingest analgesic medications during the race allowed for a meaningful assessment (i.e. not a fishing expedition) of risks associated with analgesic ingestion during a marathon and half-marathon race. The information presented in this paper is relevant to the health and safety of distance runners and a novel addition to the existing literature on the topic.</p> <p>The downside of such a large data set, however, is that sometimes the complex statistical analyses become cumbersome, especially when not explained clearly. Accordingly, there are too many tables that are difficult to interpret and should either be explained more clearly or removed. A generalized summary plus the (numerous) figures that are presented seem to tell the most important story. Inclusion of the entire analysis in such detail within the Tables detracts from the main conclusions, from my humble perspective.</p> <p><b>Specific Comments:</b></p> <p>Introduction section, page 4, line 18: References 11 and 12 do not directly pertain to adverse cardiovascular events. These investigations focused on hyponatremia which is a fluid and electrolyte imbalance. Hyponatremia is not an "adverse CV" event, as later defined under the section on outcome measures as "arrhythmias and palpitations". Thus, citing these articles here offers tenuous support, particularly since BNP and/or cardiac troponins</p>

	<p>were not measured in either of these studies (an entirely separate point of contention).</p> <p>Under Study design, page 5, line 3-4: I assume that the questionnaire was given only post-race but within what time frame (i.e. 2 weeks after race day)? Can you comment on recall bias and the window of time such errors can be minimized?</p> <p>Under Statistical analysis, page 5, line 25-26: Please describe how you categorized high and low dosages (as designated in the legend for Table 2). I assume “high dose” represents a prescription dose and “low dose” represents a typical OTC dosage (below a prescription dose). At one point in the discussion, a “supra-therapeutic” dose was mentioned but not defined. Such definitions should be stated explicitly in this section.</p> <p>Under Background epidemiology, pages 5-6: I found Table 1 to be quite confusing. Either describe the data presented in the table in greater detail or summarize key findings in this section and remove Table 1.</p> <p>Under Medication use before racing, page 6: It is unclear how many athletes took analgesics before the race BECAUSE they started the race with a prior injury/or pain. This may bias the reported outcomes of AE’s. If this information is indeed reported, it needs to be emphasized.</p> <p>Under Events during and after the race, pages 7, lines 13-16: Please go into greater detail somewhere in the text with regards to what is meant by “unspecified CV/AE’s”. What questions were specifically asked? Chest tightness? Palpitations??Difficulty breathing??</p> <p>Discussion section, page 9, line28: what is meant by “unsuitable” drug?</p> <p>Table 1: Again, I found this table difficult to understand. Are the data presented as numbers plus the percentages of the sub-population in parentheses? Generally, standard deviations or standard errors are presented in parentheses; thus the confusion (because above there is only “%” in parentheses). Then, on my version, the words are broken-up in odd places. Summarize the take home message or make this data exquisitely clear within the Table without cumbersome legends.</p> <p>Table’s 2-4 are best suited as figures, and since the figures and tables are redundant, I advise removing these Tables.</p> <p>Do all the bar graphs represent combined data from the half and full marathon? What about the last figure regarding the dosages?</p>
--	---

<b>REVIEWER</b>	<p>Dr Juan Manuel Alonso MD, PhD          Head of Medical Department          Royal Spanish Athletics Federation, Madrid. Spain          Medical and Anti-doping Commission Chair          IAAF, Monaco          Conflict of interests: None.</p>
<b>REVIEW RETURNED</b>	10-Nov-2012

<b>THE STUDY</b>	<p>A preliminary question I raise to the authors is the adequacy of the term Analgesic. To me it would be much more appropriate to use the term NSAID instead. I strongly suggest the authors to consider replacing analgesics by NSAIDs not only in the title but in the abstract and text. As authors themselves state, the correct design to answer the research question would have been a double-blind randomized control trial. However, not only seems impractical to implement a RCT but ethical questionable. If we expect higher rates of adverse effects in runners consuming NSAIDs it wouldn't be proper to prescribe them their use prior to the race. This makes this topic difficult and is a major argument in favors of the design choice by authors.</p> <p>I would recommend the authors to describe in the text the way they approached the study population. There is no information whether they invited the participants to fill in the questionnaire (electronically, by telephone or by personal interview). You mention at P9, L10-12 that reporting was spontaneous and voluntary. You better insert this information on Methods section. I also miss in the Methods section the information on how you informed the participants to fill in the questionnaire and how to report important adverse events after the race such as hospital admittances.</p> <p>I would suggest the authors to insert and comment in Discussion section a couple of citations:  Tscholl PM, Dvorak J. Abuse of medication during international football competition in 2010 – lesson not learned. Br J Sports Med 2012. doi: 10.1136/bjsports-2011-090806  And the authors own reference (I would suggest to insert it at Page 9, L26-27):  Brune K, Niederweis U, Kaufmann A, Küster-Kaufmann M. [Drug use in participants of the Bonn Marathon 2009]. MMW Fortschr Med. 2009 Oct 1;151(40):39-41</p> <p>I would advise authors to describe better the in the text (P6, L3-7) the description of the two sub-groups: state that the age means are from analgesics vs. non-analgesics subgroups.</p> <p>To me the sentence on page 8 L46-49 does not clearly states whether you mean that there was one single case of bleeding ulcer or more. Please, reword this sentence to enable easier understanding.</p> <p>Page 10, L19, please insert “from” to read “...do not prevent from pain”.</p> <p>On the Limitations Bullet Point no 4 (P11, L52) I miss the information on why the authors did not register nor investigated weight, height, Body Mass Index (BMI) and use of other drugs. Having no information on hospital admittances in the non-analgesic group is an important limitation of the study which I recommend the authors to include in this section as well as an explanation on whether or not the authors requested this subgroup to report this important information and, if not, why.</p> <p>Please replace the word “hospitalization” by “hospital admittances”.</p>
<b>REPORTING &amp; ETHICS</b>	<p>Despite the authors state in the text P12, L58-59, under Acknowledgements, that there were not ethical issues being an observational study, I question this statement. When reporting experiments on human subjects, authors should always indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Authors did not provide such information on the text, nor whether they get ethical approval for the study or inform consent from the participants.</p>
<b>GENERAL COMMENTS</b>	<p>I would like to congratulate authors for the excellent job. They</p>

	performed an original research of a very interesting topic that can have an important impact on recreational runners' health. As authors themselves state, the correct design to answer the research question would have been a double-blind randomized control trial. However, not only seems impractical to implement a RCT but ethical questionable. If we expect higher rates of adverse effects in runners consuming NSAIDs it wouldn't be proper to prescribe them their use prior to the race. This makes this topic difficult and is a major argument in favors of the design choice by authors.
--	--

<b>REVIEWER</b>	Eduardo Cadore Department of Health Sciences, Public University of Navarre, Navarre, Spain
<b>REVIEW RETURNED</b>	13-Nov-2012

<b>THE STUDY</b>	The authors did not mentioned the similar study of Gorski et al. 2009, who investigated the prevalence, reasons for use and level of awareness of NSAIDs among athletes participating in an Iron Men race. Thus, the authors are kindly asked to update the literature of the manuscript. In addition, some of the references cited did not investigate the issues mentioned by the authors. For example, the references 11 and 12 did not investigate cardiovascular events as mentioned (only hyponatremia).
<b>RESULTS &amp; CONCLUSIONS</b>	The authors did not mentioned relevant similar studies. Thus, the discussion must be improved relating the results to previous evidence. In doing so, the authors should improve the clinical relevance description of their results.
<b>REPORTING &amp; ETHICS</b>	No reporting statement or checklist related to CONSORT registration was found in the manuscript.
<b>GENERAL COMMENTS</b>	<p>The purpose of this study was report use of analgesic drugs and its dose in relation to premature race withdrawal, and the side-effects occurring during and after racing. This paper deals with an issue not frequently addressed in the international scientific literature. The study is concisely and well written and the data presented are of particular interest for the sports scientists and fitness coaches. However, there are some important points that need to be addressed before the manuscript could be considered for publication.</p> <p>Specific comments</p> <p>Firstly, the authors mentioned that this is the first study which related unwanted drug effects during endurance sports to the use of analgesics. However, the authors did not mentioned the similar study of Gorski et al. 2009, who investigated the prevalence, reasons for use and level of awareness of NSAIDs among athletes participating in an Iron Men race. Thus, the authors are kindly asked to update the literature of the manuscript.</p> <p>What are the primary novelties of the study? The authors are kindly asked to justify better the study. What does this study bring of novelty that the literature has not addressed yet? In this way, what is the main clinical application of the study?</p> <p>Page 4, line 18: Some of the references cited did not investigate the issues mentioned by the authors. For example, the references 11 and 12 did not investigate cardiovascular events as mentioned (only hyponatremia). Please, revise all the reference according with their content.</p>

	<p><b>Methods</b> Was the questionnaire previously validated? The subjects were capable to understand concepts as “haematuria” and “arthralgia”?</p> <p>The authors asked the athletes about the use before the marathon. Why do not ask about the use DURING the marathon. Some of the “non-users” athletes may not have used before, but they may have used during...</p> <p><b>Discussion</b> Page 9, line 21: Again, the reference 11 investigated hyponatremia, which is related to cardiovascular events. However, to define hyponatremia as cardiovascular event seems a little “strong” because cardiovascular events during this kind of race may result of other reasons (please, see the reference: M. Mouallem M.D., E. Friedman M.D., Y. Shemesh M.D., H. Mayan M.D., R. Pazner M.D., Z. Farfel M.D.).</p> <p>Page 21, lines 31-36: “worrying lack of education (...), which may highlight a larger problem if mirrored in the endurance sports community in general”, corroborates with the study of Gorski et al. 2009 - BJSM).</p>
--	--

### VERSION 1 – AUTHOR RESPONSE

We have amended our manuscript according to the suggestions (see enclosed text). In particular, the following changes were made:

- Following the suggestion of referee 1, we have inserted all the tables with one notable exception into the section of supplementary materials. This allows for grasping the context of the investigation more easily. In addition it gives access to all details not provided in the figures. Consequently the text of the introduction, methods and results section had to be amended.
- We have added two more quotes, as suggested by referee 3. We want to point out, that Gorski's results were published later than ours. In these earlier investigations Gorski and we could not relate the incidence of adverse events during sports activities to the use of non-steroidal, anti-inflammatory drugs. This is the merit of the present manuscript.
- We agree with the referees that hyperhydration or dehydration do not constitute cardiovascular events. Consequently, we have amended the text accordingly. Under these conditions, the 2 quotes referring to electrolyte disturbances during marathon running are now in the right place.
- We have described the procedures of distributing and collecting the questionnaires for evaluation in more detail. We have also defined the procedures to avoid that the anonymity of the participants can be broken. Also the time frame used was specified. We want to point out that the last questionnaire received by us was 3 weeks after the race. More importantly, 90% of the questionnaires were received within the fortnight after the race.
- Wherever possible, we categorized dosing according to the permitted OTC single dose as “low”, all others were regarded as “high”. Within “high” doses we referred to “supra-therapeutic doses” which means that the permitted maximum daily dose for prescription was exceeded. This dose was defined as “supra-therapeutic”. With “unsuitable drugs” we refer to cyclooxygenase inhibitors with an extensively slow elimination half-life, as e.g. piroxicam. May be this is not a meaningful term within this manuscript. It could lead away from the focus of the paper and we therefore eliminated this expression.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Dr Juan Manuel Alonso MD, PhD Head of Medical Department, Royal Spanish Athletics Federation, Madrid, Spain Chair of Medical and Anti-doping Commission, International Association of Athletics Federations, Monaco
<b>REVIEW RETURNED</b>	19-Dec-2012

<b>GENERAL COMMENTS</b>	<p>My preliminary question to the authors on the adequacy of the term Analgesic has not even been replied. To me it would be much more appropriate to use the term NSAID instead. I strongly suggest the authors to consider replacing analgesics by NSAIDs not only in the title but in the abstract and text.</p> <p>I would suggest the authors to insert and comment in Discussion section citation (from the same authors!):</p> <p>And the authors own reference (I would suggest to insert it at Page 10, L10-12):</p> <p>Brune K, Niederweis U, Kaufmann A, Küster-Kaufmann M. [Drug use in participants of the Bonn Marathon 2009]. MMW Fortschr Med. 2009 Oct 1;151(40):39-41</p> <p>To me the sentences on page 9 L28-32 “Four respondents (numbers 4-7, Tables S4) reported hospitalisation because of GI-bleeding (black stools and vomiting blood. Gastroscopic evaluation revealed at least one bleeding in all four respondents” does not clearly state whether you mean that there was one single case of bleeding ulcer or four. According to table S4 there were two bleeding cases (no 4 and 7). Please, reword this sentence to enable easier understanding.</p> <p>On the Limitations Bullet Point no 4 (P11, L52) I miss the information on why the authors did not register nor investigate weight, height, Body Mass Index (BMI) and use of other drugs. Having no information on hospital admissions in the non-analgesic group is an important limitation of the study which I recommend the authors to include in this section as well as an explanation on whether or not the authors requested this subgroup to report this important information and, if not, why.</p> <p>I again strongly encourage authors to replace the word “hospitalization” by “hospital admissions”.</p>
-------------------------	---

<b>REVIEWER</b>	Eduardo Lusa Cadore, Associate researcher, Department of Health Sciences, Public University of Navarre, Spain
<b>REVIEW RETURNED</b>	04-Dec-2012

<b>GENERAL COMMENTS</b>	The manuscript has been successfully improved.
-------------------------	--

## VERSION 2 – AUTHOR RESPONSE

Reviewer: Dr Juan Manuel Alonso MD, PhD  
Head of Medical Department,  
Royal Spanish Athletics Federation, Madrid, Spain  
Chair of Medical and Anti-doping Commission,  
International Association of Athletics Federations, Monaco

My preliminary question to the authors on the adequacy of the term Analgesic has not even been

replied. To me it would be much more appropriate to use the term NSAID instead. I strongly suggest the authors to consider replacing analgesics by NSAIDs not only in the title but in the abstract and text.

We agree with the reviewer that the majority of cyclooxygenase-inhibitors (COX-inhibitors) can be summarized as non-steroidal anti-inflammatory drugs (NSAIDs). However, we prefer to use the term “analgesic” in the title, text and figures because other analgesics (e.g. acetaminophen and dipyron) are also known to inhibit COX-enzymes but did not show substantial anti-inflammatory action. Therefore we added the reason for using “analgesics” at the end of the introduction.

I would suggest the authors to insert and comment in Discussion section citation (from the same authors!):

And the authors own reference (I would suggest to insert it at Page 10, L10-12):  
Brune K, Niederweis U, Kaufmann A, Küster-Kaufmann M. [Drug use in participants of the Bonn Marathon 2009]. MMW Fortschr Med. 2009 Oct 1;151(40):39-41

The reference is added now.

To me the sentences on page 9 L28-32 “Four respondents (numbers 4-7, Tables S4) reported hospitalisation because of GI-bleeding (black stools and vomiting blood. Gastroscopic evaluation revealed at least one bleeding in all four respondents” does not clearly states whether you mean that there was one single case of bleeding ulcer or four. According to table S4 there were two bleeding cases (no 4 and 7). Please, reword this sentence to enable easier understanding.

We have reworded the sentence for clarification.

On the Limitations Bullet Point no 4 (P11, L52) I miss the information on why the authors did not register nor investigated weight, height, Body Mass Index (BMI) and use of other drugs. Having no information on hospital admittances in the non-analgesic group is an important limitation of the study which I recommend the authors to include in this section as well as an explanation on whether or not the authors requested this subgroup to report this important information and, if not, why.

As suggested by the reviewer we have added the reason for the limited number of items used in the questionnaire.

Due to the study design and ethical reasons (integrity of participants and data protection) it was not possible to document data for hospital admission with corresponding reference data on the questionnaire. Therefore we decided to use spontaneous and voluntary reports transferred to the physician. We addressed this issue at the end of the result section.

I again strongly encouraged authors to replace the word “hospitalization” by “hospital admittances”.

We have replaced hospitalization throughout the manuscript.