



**Consumption of analgesics before a marathon increases the incidence of cardiovascular, gastrointestinal, and renal problems in a dose-dependent manner**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002090
Article Type:	Research
Date Submitted by the Author:	12-Sep-2012
Complete List of Authors:	Kuester, Michael; Schmerzzentrum DGS, Renner, Bertold; FAU Erlangen-Nuremberg, Department of Experimental and Clinical Pharmacology and Toxicology Oppel, Pascal; FAU Erlangen-Nuremberg, Niederweis, Ursula; Universtitaetsklinikum Erlangen, Anaesthesiologische Klinik Brune, Kay; FAU Erlangen-Nuremberg, Department of Experimental and Clinical Pharmacology and Toxicology
<b>Primary Subject Heading</b>:	Sports and exercise medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	PUBLIC HEALTH, SPORTS MEDICINE, Adverse events < THERAPEUTICS

SCHOLARONE™  
Manuscripts

1  
2  
3 **Consumption of analgesics before a marathon increases the incidence of**  
4 **cardiovascular, gastrointestinal, and renal problems in a dose-dependent**  
5 **manner**  
6  
7  
8  
9

10  
11 M. Küster<sup>#</sup>, B. Renner<sup>#</sup>, P. Oppel, U. Niederweis, K. Brune<sup>\*</sup>  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

42 \* Corresponding author

43  
44  
45 # Both authors contributed equally to the manuscript.  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### *Article focus*

- The participation in endurance sports, as marathon, is growing worldwide.
- Many amateurs engage in occasional endurance activities without adequate training, medical information, and experience.
- They try to overcome pain during and after sports by taking OTC-analgesics.

### *Key message*

We hypothesized that the drugs taken before sports may increase the incidence of CV, GI and kidney damage without lowering pain during and after the exercise. An evaluation of about 4000 participants in a marathon resp. half-marathon supports this contention. Serious unwanted events occurred predominantly in users of analgesics. A benefit was not apparent.

### *Strengths and limitations of this study*

This is the first investigation which relates unwanted drug effects during endurance sports to the use of analgesics. The effect was significant at OTC-doses and increased with higher doses. The incidence of organ damage was about eight times more frequent after analgesic use. Serious events requiring hospitalization were reported only in the analgesic group. These findings pinpoint the unexpected risk of the prophylactic use of these drugs in sports.

In our study, the role of confounders, as preexisting joint pain, could not be excluded.

1  
2  
3 *Abstract*  
4

5 **Objectives:** To prevent pain inhibiting their performance, many athletes ingest over-  
6 the-counter (OTC) analgesics before competing. We aimed at defining the use of  
7 analgesics and the relation between OTC analgesic use/dose and adverse events  
8 (AEs) during and after the race, a relation that has not been investigated to date.  
9

10  
11  
12 **Design:** Prospective (non-interventional) cohort study, using an on-line questionnaire  
13

14  
15 **Setting:** The Bonn marathon 2010  
16

17  
18 **Participants:** 3,913 out of 7,048 participants in the Bonn marathon 2010 returned  
19 their questionnaires.  
20

21  
22 **Primary and secondary outcomes:** Intensity of analgesic consumption before  
23 sports; Incidence of adverse events in the cohort of analgesic users as compared to  
24 non-users.  
25

26  
27 **Results:** There was no significant difference between premature race withdrawal rate  
28 in the analgesics cohort and the cohort who did not take analgesics ('controls').  
29 However, race withdrawal because of gastrointestinal (GI) AEs was significantly more  
30 frequent in the analgesics cohort than in the control. Conversely, withdrawal because  
31 of muscle cramps was rare, but significantly more frequent in controls. The  
32 analgesics cohort had an almost ten times higher incidence of AEs (overall risk  
33 difference 13%). This incidence increased significantly with increasing analgesic  
34 dose. Nine respondents reported temporary hospitalisation: three for temporary  
35 kidney failure (post ibuprofen ingestion), four with bleeds (post aspirin ingestion), and  
36 two cardiac infarctions (post aspirin ingestion). None of the control reported  
37 hospitalisation.  
38  
39  
40  
41  
42  
43  
44  
45

46  
47 **Conclusions:** The use of analgesics before participating in endurance sports may  
48 cause many, potentially serious, unwanted AEs that increase with increasing  
49 analgesic dose. Analgesic use before endurance sports appears to pose an  
50 unrecognized medical problem as yet. If verifiable in other endurance sports, it  
51 requires the attention of physicians and regulatory authorities.  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Introduction

Endurance sports are becoming increasingly popular. However, recent research has shown that physical activity does not automatically result in better health, but could exacerbate cardiovascular (CV) disease<sup>1,2</sup>. This may be related to the inhibition of cyclooxygenases by non-steroidal inflammatory drugs (NSAIDs), including 'over the counter' (OTC) analgesics, that are known to exacerbate atherosclerosis<sup>3</sup> and CV problems in some patients<sup>4</sup>.

Previous studies have shown that the use and abuse of analgesics in sports is frequent and possibly dangerous<sup>5-10</sup>, and that the incidence and severity of CV<sup>11,12</sup>, gastrointestinal (GI)<sup>13</sup>, and renal adverse events (AEs)<sup>14-16</sup> during and after racing double after taking analgesics. However, these studies investigated AEs in isolation and did not investigate a dose response relationship.

In a preliminary study, we interviewed 1,024 participants of the Bonn marathon/half marathon, and collected information on their training, fitness, and drug use<sup>5</sup>. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice<sup>5</sup>.

We now report a follow-up study of analgesic use and dose in relation to premature race withdrawal, and AEs occurring during and after racing.

## Methods

### Study population

The investigation relied on a questionnaire, available to all participants of the Bonn marathon/half marathon 2010 on paper and via the internet (Figure 1). The questionnaire examined:

1. Background epidemiology: age, sex, running experience, use of analgesics during training/in previous races, and details of previous training.
2. Medication use before the race: name and dose of drugs taken before the race start, and any medical advice received.
3. During and after racing: completion/reasons for premature withdrawal from the race, and AEs.

### Study design

1  
2  
3 All data were submitted by internet or email, and were checked for completeness  
4 using SPSS software version 19, followed by inspection by two researchers.  
5  
6

### 7 **Outcome measures**

8  
9 The primary hypothesis was that consumption of analgesics is associated with an  
10 increased incidence of AEs. An AE was included in the analysis if one or more of the  
11 following events were recorded on the questionnaire: GI cramps and bleeds,  
12 haematuria, or CV events (e.g. arrhythmia, palpitation).  
13  
14  
15  
16

### 17 **Statistical analysis**

18  
19 AEs and reasons for premature race withdrawal were tabulated according to a  
20 number of population-based factors which may influence drug use or AE incidence.  
21 Cross-tables, the chi square test, or Fisher's test were used to analyse subgroups to  
22 establish relative risk differences and possible confounding factors. Drug doses (no  
23 drug, low dose, and high dose) were used to determine possible dose-related effects  
24 on AE incidence and race withdrawal.  
25  
26  
27  
28  
29

30 A binary regression model was used to estimate odds ratios and 95% confidence  
31 intervals for AE incidence in subgroups and in the primary study population, with  
32 adjustment for confounding factors. Analyses were conducted using SPSS software  
33 version 19. Statistical tests were two-sided, and p-values less than 0.05 were  
34 considered statistically significant. AEs from respondents who did not state which  
35 race they entered were not included in the marathon/half marathon sub-group  
36 analysis.  
37  
38  
39  
40  
41  
42

### 43 **Results**

44 4,268 completed questionnaires were returned. Approximately 4% were identified as  
45 duplicates, and were excluded from the analysis. An additional 4% of questionnaires  
46 were excluded because primary data were missing (i.e. age, sex, drug use, AEs).  
47  
48  
49

50 The remaining 3,913 completed questionnaires constituted the primary study  
51 population, representing 56% of the participants in the Bonn marathon/half marathon  
52 2010 (Figure 2).  
53  
54  
55

### 56 Background epidemiology

1  
2  
3 Descriptive epidemiological data are given in Table 1. Overall, there were more men  
4 than women (2,376 vs. 1,537), and men were slightly older on average (means: 38  
5 and 43 years vs. 34 and 42 years).  
6  
7

8  
9 A larger proportion of men used analgesics during training. Most respondents (66-  
10 99%) had previous marathon experience. In the group who took analgesics before or  
11 during the marathon/half marathon ('analgesics cohort'), 14-26% had taken  
12 analgesics during training, compared with 1% of the group who did not take  
13 analgesics ('controls'). Of the analgesics cohort, 5-17% recorded pain before the race  
14 (compared with 1-2% of controls), and 14-18% recorded AEs during/after racing  
15 (compared with 2-7% of controls).  
16  
17  
18  
19

### 20 21 Medication use before racing

22  
23 In total, 1,931 respondents ingested analgesics before racing, to retard or avoid pain  
24 during the races and thereafter. Nearly half of the respondents (49%) used  
25 analgesics immediately before the race, most of which (54%) were taken without  
26 medical prescription (Table 2), and significantly more women took analgesics than  
27 men (Table1).  
28  
29  
30  
31

32  
33 The most frequently used analgesic was diclofenac, used by 47% of the analgesics  
34 cohort before the race (Table 2). Many athletes (11%) resorted to supra-OTC doses  
35 of diclofenac (over 100 mg). The second most commonly used analgesic was  
36 ibuprofen, and 43 % of those who took ibuprofen ingested  $\geq 800$  mg (twice as the  
37 recommended OTC single dose). Aspirin was used less frequently, and mostly at  
38 therapeutic doses. Acetaminophen, celecoxib, dipyron, etoricoxib, meloxicam, and  
39 naproxen were also used, although these drugs were taken by comparatively few  
40 athletes and are grouped as 'other analgesics' in the analysis (Table 2).  
41  
42  
43  
44  
45

46  
47 Of all respondents, 93% had not been informed about the risks of using analgesics in  
48 connection with sport (Table 1).  
49

### 50 51 Events during and after the race:

52  
53 The incidence of AEs was significantly higher in runners of the full marathon  
54 compared with the half-marathon (18% vs 7%;  $p < 0.001$ ). Additionally, the analgesic  
55 related AE risk in the full marathon cohort was significantly higher than in the half  
56 marathon cohort (odds 9.04; 95% CI 5.31-15.39 vs 3.20; CI 2.32-4.42. Figure 3).  
57  
58  
59  
60

1  
2  
3 There were similar numbers of half marathon and marathon runners in the analgesics  
4 cohort compared with controls. A four to ten times higher incidence of each type of  
5 AE was observed in the analgesics cohort compared with controls (overall incidence  
6 4% vs 16%. Table 3, Figure 4), with a calculated risk difference of 13%. The  
7  
8 difference in the incidence of AEs between the two cohorts was most prominent with  
9  
10 respect to GI cramps and CV-events (after race). In the analgesics cohort, GI cramps  
11  
12 were the most frequent AE (reported by 14% of the cohort), followed by (unspecified)  
13  
14 CV AEs after the race (9%). In the controls, (unspecified) CV AEs after the race were  
15  
16 the most frequently reported AE (3%, Table 3). Notably, haematuria occurred only in  
17  
18 the analgesics cohort. The differences in the incidence of all AEs were highly  
19  
20 significant between the two groups ( $p < 0.001$ , Table 3, Figure 4).

21  
22 No significant difference was found between the analgesics cohort and controls in  
23  
24 premature race withdrawal overall (Table 3,  $p = 0.237$ ). Race withdrawal because of  
25  
26 muscle cramps occurred significantly more often in controls (3% vs 1%, Table 3,  
27  
28 Figure 5,  $p < 0.001$ ), but the absolute difference was small. Conversely, intestinal  
29  
30 cramps were significantly more frequently blamed for race withdrawal in the  
31  
32 analgesics cohort compared with controls (2% vs 1%;  $p < 0.01$ , Table 3, Figure 5).

33  
34 Joint and muscle pain after the race were significantly more frequent in the  
35  
36 analgesics cohort than in controls (1,301 vs 955 respondents,  $p < 0.001$ , Table 3,  
37  
38 Figure 6).

39  
40 The overall risk for analgesic related AEs was estimated at 5.1 (95% CI 3.9-6.7;  
41  
42  $p < 0.001$ , Figure 7), giving a 'number needed to harm' of eight treated people. In a  
43  
44 subsequent subgroup analysis for sex, age, training, marathon/half marathon run,  
45  
46 and analgesic experience, an enhanced risks (odds ratio) for the different subgroups  
47  
48 was detected, but this was very variable (1.6-13.4, Figure 3). Therefore, these  
49  
50 subgroup parameters were included in a regression analysis which resulted in a  
51  
52 comparable adjusted analgesic related risk of 3.0 (95% CI 2.1-4.1;  $p < 0.001$ , Figure  
53  
54 7).

55  
56 To investigate if the incidence of AEs was dose-dependent, a risk estimation of the  
57  
58 size of the dose was conducted. The high dose resulted in a significantly higher risk  
59  
60 of AEs compared with the lower dose or controls. Even the low dose group presented  
a higher risk of AEs compared with controls (Figure 7). This further adjusted



1  
2  
3 regression model showed a statistically significant increased risk at rising doses,  
4 meaning that increasing the dose can increase the risk of AEs by three times (odds  
5 ratio 3.2; 95% CI, 2.7-4.0,  $p < 0.001$ , Figure 7).  
6  
7

8  
9 Finally, the association of analgesic use with distinct side effect profiles was  
10 analysed. The ingestion of all three drugs (aspirin, diclofenac, and ibuprofen) was  
11 associated with AEs in a dose-dependent manner (Table 4). Overall, the incidence  
12 (defined as the percentage of respondents reporting AEs out of the total number of  
13 respondents taking a particular analgesic) was highest with aspirin, followed by  
14 ibuprofen, and lowest with diclofenac in both subgroups (high and low dose of  
15 analgesics. Table 4). At high doses, 10% of diclofenac users, 52% of ibuprofen  
16 users, and 87% of aspirin users experienced AEs (Table 4). Aspirin was associated  
17 with relatively numerous GI or kidney bleeds, compared with the other analgesics.  
18  
19  
20  
21  
22  
23

### 24 **Serious cases**

25  
26  
27 In addition to the evaluation by questionnaire, the participants of the Bonn  
28 marathon/half marathon 2010 were asked to report serious events which required  
29 hospitalisation during the 3 days following the race. Nine reports of hospitalisation  
30 were received (Table 5), all of which concerned respondents from the analgesics  
31 cohort. Three athletes (numbers 1-3, Table 5) reported anuria/oliguria which started  
32 the day after the race and lasted for up to three days. In two cases this AE resolved  
33 after a hyperuric period, and one respondent reported ongoing renal problems  
34 (haematuria for 2 days - number 3, Table 5). In all three cases, moderate doses of  
35 ibuprofen (2 x 400 mg, 600 mg, and 600 mg) were taken before and during the race  
36 together with large amounts of fluid.  
37  
38  
39  
40  
41  
42  
43

44 Four respondents (numbers 4-7, Table 5) reported hospitalisation because of GI-  
45 bleeding (black stools and vomiting blood). Gastroendoscopic evaluation revealed at  
46 least one bleeding ulcer in all four respondents. They were treated endoscopically  
47 and given proton pump inhibitors. All four respondents had ingested moderate  
48 amounts of aspirin (500-1,000 mg) before the race, and all were released after a few  
49 days without obvious sequelae.  
50  
51  
52  
53  
54

55 Two more respondents (numbers 8 and 9, Table 5) were hospitalised after ingesting  
56 aspirin before the race. One took a 100 mg dose to prevent infarction, the other took  
57 500 mg because of mild foot pain. Both respondents complained of chest pain,  
58  
59  
60

1  
2  
3 angina, and arrhythmia the day after racing, and both suffered cardiac infarctions.  
4 Both athletes recovered, although some cardiac damage remained in one  
5 respondent.  
6  
7

8  
9 These nine cases are well documented (Table 5). However, it should be noted that  
10 since reporting was spontaneous and voluntary, and a lack of corresponding  
11 hospitalisations in the control cohort could not be proven.  
12  
13

### 14 **Discussion**

15  
16  
17 It is known that many professional and amateur athletes use analgesics  
18 prophylactically to increase performance and prevent pain<sup>6-8,18</sup>.  
19  
20

21 A recent publication in the NEJM<sup>11</sup> warned that over-hydration during marathons  
22 might increase the risk of CV events. However, this study did not investigate the  
23 association between the use of drugs and CV problems. Recently, we reported that  
24 two-thirds of the participants of a marathon took analgesics before the start. This  
25 investigation showed that most athletes taking analgesics had either taken unsuitable  
26 drugs or supra-therapeutic doses. However, the study did not investigate the use of  
27 analgesics and premature race withdrawal, nor did it systematically record  
28 performance and incidence of AEs.  
29  
30  
31  
32  
33  
34

35 The current study was designed to test the hypothesis that cyclooxygenase inhibitors  
36 contribute to the development of AEs, which is possible since these drugs block the  
37 protective effects of prostaglandins on GI, CV, and renal function. We hypothesise  
38 that their use is likely to suspend the mucosa- and kidney-protective<sup>3</sup> effects of  
39 PGE<sub>2</sub>/PGI<sub>2</sub>, thus augmenting the damaging effect of diminished blood flow<sup>19</sup> and  
40 oxygen supply for the GI mucosa and kidney<sup>20</sup>. Moreover, it was postulated that  
41 marathon runs could decrease the barrier function of the intestinal mucosa, further  
42 increasing the absorption of bacterial toxins from the gut<sup>21</sup>, and that repeated  
43 inhibition of the production of endothelium-produced PGI<sub>2</sub> during CV stress, e.g.  
44 intensive exercise, may accelerate atherosclerosis<sup>1,2,22</sup>.  
45  
46  
47  
48  
49  
50  
51

52 This study analysed respondents for age, sex, training status, drug use (including  
53 doses), race completion, and AEs that occurred during the race and afterwards. To  
54 the best of our knowledge, this study shows for the first time that the administration of  
55 analgesics before a marathon/half-marathon can significantly increase AEs, and  
56  
57  
58  
59  
60

1  
2  
3 these increase with increasing analgesic dose. This increased incidence of AEs is  
4 dramatic; e.g. 4% of respondents in the analgesics cohort reported haematuria  
5 compared with 0% of controls. Moreover, nine respondents reported hospitalisation  
6 caused by either temporary kidney failure, bleeding ulcers, or cardiac infarctions. All  
7 these serious events occurred in the analgesics cohort.  
8  
9

10  
11 Altogether, these data do not support the contention that taking analgesics before  
12 racing improves the ability to complete the race or to prevent AEs thereafter.  
13  
14

15  
16 Four aspects of this study deserve an in-depth discussion.  
17

18  
19 1. *Analgesics taken prophylactically before racing do not prevent pain*

20 Analysis of the pain reported by respondents before and after racing showed  
21 no major identifiable advantages gained from taking analgesics. Muscle  
22 cramps were reported as a reason for premature race withdrawal marginally  
23 less frequently in the analgesics cohort compared with the control. Although  
24 the difference was significant ( $p < 0.001$ ), the small sample size does not allow  
25 concrete conclusions to be drawn, particularly in the context of the parameters  
26 of overall pain during racing and intestinal cramps. There were significantly  
27 more intestinal cramps in the analgesics cohort ( $p < 0.001$ ) compared with the  
28 control, and more muscle and joint pain were reported in the analgesics cohort  
29 after racing than in the control.  
30  
31  
32  
33  
34  
35  
36

37 This result supports observations reported by Nieman *et al.*, who found that  
38 the intake of ibuprofen at regular intervals during an ultra-marathon race did  
39 not decrease muscle soreness in the days afterwards<sup>23</sup>. This may be  
40 explained by the fact that all the drugs investigated (diclofenac, ibuprofen, and  
41 aspirin) display a short elimination half-life of around two hours, which would  
42 make effects several hours after the ingestion of the drugs rather unlikely. In  
43 the report by Nieman *et al.*, the last dose of ibuprofen was taken a few hours  
44 before finishing the race, and so the lack of influence on post-race pain is not  
45 surprising. Several research groups have reported the analgesic effects of  
46 NSAIDs in volunteers undertaking physical exercise. However, in these  
47 studies, the drugs were given after exercise, not before, which makes their  
48 reported analgesic effect plausible and recognisable<sup>24-26</sup>.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 In conclusion, our data indicate that the intake of cyclooxygenase inhibitor  
4 analgesics does not offer protection from pain during or after a marathon/half  
5 marathon compared with controls. However definitive proof of this contention  
6 would warrant a prospective, randomised cohort study.  
7  
8  
9

## 10 2. *Analgesics contribute to AEs*

11 This study investigated if cyclooxygenase inhibitors contribute to the AEs  
12 observed frequently in endurance sports<sup>21,27</sup>. All of the AEs observed  
13 frequently during marathons, i.e. CV events, GI cramps/bleeds, and renal  
14 dysfunction, occurred much more frequently in the analgesics cohort  
15 compared with the control. This effect was not dependent on the type of  
16 analgesic, i.e. all three drugs caused an increase in CV, GI, and renal AEs.  
17 This supports our hypothesis that the use of cyclooxygenase inhibitors before  
18 the start of a race may be damaging because tissue protection that is usually  
19 provided by prostaglandins may be impaired, triggering GI, CV, and renal AEs.  
20 These effects again suggest that the use of cyclooxygenase inhibitors before  
21 and during a marathon/half marathon race may be dangerous and should be  
22 avoided.  
23  
24  
25  
26  
27  
28  
29  
30  
31

## 32 3. *The AE profile of different analgesics is different*

33 Although the use of analgesics increases the overall incidence of AEs, all nine  
34 serious events reported to us which led to temporary hospitalisation concur  
35 with the pattern of AEs seen per drug in the rest of the respondents. The three  
36 temporary kidney failure cases (all of whom had ingested ibuprofen)  
37 correspond with the relatively high incidence of renal AEs in the ibuprofen  
38 group (Table 5, Table 4). Moreover, the bleeding ulcers observed in the aspirin  
39 group mirror the high incidence of GI problems seen after the intake of aspirin.  
40 Somewhat surprising is the fact that both cardiac infarctions occurred in the  
41 aspirin group. This is interesting since aspirin should have protected from such  
42 events. However, definite conclusions cannot be drawn because of the small  
43 sample size. Overall, our observations are in line with previous reports<sup>1,28-30</sup>.  
44  
45  
46  
47  
48  
49  
50  
51

## 52 4. *Limitations of the study*

53 A double-blind, randomized, cross-over design for any trial is the gold  
54 standard. However, this is obviously impractical in these circumstances.  
55 Despite the relatively high return of questionnaires, there was still no  
56 information available for half of the marathon/half marathon participants, and  
57  
58  
59  
60

1  
2  
3 many confounding factors such as BMI, use of other drugs etc. were not  
4 investigated. Although the two cohorts were of similar sizes, there are  
5 differences between them with respect to age, sex, training, and drug  
6 experience (a contribution of long term use of OTC analgesic on the incidence  
7 of AEs cannot be excluded), which may also have influenced the outcome.  
8 However, the considerable homogeneity of the AEs seen throughout all  
9 subgroups supports the overall contention that cyclooxygenase inhibitors  
10 taken before and during a marathon/half marathon race increase the risks of  
11 AEs substantially, without measurable benefit in terms of race completion.  
12  
13  
14  
15  
16  
17

18  
19 Taken together, our data indicate that the widespread use of cyclooxygenase  
20 inhibitors in connection with endurance sports is potentially damaging. In our study,  
21 the administration of analgesics before the start of a race did not prevent post-  
22 exercise pain or significantly reduce the premature withdrawal rate compared with the  
23 control. Conversely, the use of cyclooxygenase inhibitors considerably increased the  
24 incidence of GI, renal, and CV AEs. We conclude that the use of analgesics before  
25 and during endurance sports may pose a serious health problem that should be  
26 addressed. Our investigation has also shown a worrying lack of education about  
27 these AEs within the participants of the Bonn 2010 marathon/half marathon, which  
28 may highlight a larger problem if mirrored in the endurance sport community in  
29 general. We would encourage greater awareness of the possible AEs of these drugs,  
30 particularly among endurance sports enthusiasts.  
31  
32  
33  
34  
35  
36  
37  
38

39 Further investigations are warranted to examine if the use of analgesics before and  
40 during sports activities should be avoided altogether.  
41  
42  
43  
44  
45

## 46 **Acknowledgements**

47  
48 K. Brune is Doerenkamp-Professor. He was supported by the Hertie Foundation.

49 The authors declare no conflict of interest.

50  
51 The authors acknowledge the assistance of a medical writer in the editing and  
52 language checking of this manuscript.  
53  
54

55 There is no additional data available.  
56  
57

58 As our study is an observational study, there are no ethical issues.  
59  
60

1  
2  
3 Contributorship Statement: MK and BR organized and evaluated the questionnaire. They also did  
4 the necessary calculations. PO and UN organized the data and prepared them for statistical  
5 evaluation. KB had the idea to investigate the use and abuse of cyclooxygenase inhibitors in amateur  
6 sports. He also posed the hypothesis that the use of these drugs during endurance sports aggravates  
7 the risks of cardiovascular, gastrointestinal, and kidney problems. He also wrote most of the  
8 manuscript.  
9

10 Funding Statement: Funded by Hertie Foundation.  
11

12 Competing Interests Statement: All authors have no conflict of interest. The results of this  
13 investigation do not support the use of certain drugs, but rather point out that all so called  
14 cyclooxygenase inhibitors, taken before endurance sports, may carry serious risks. Patient consent  
15 appears not required as all patients remain anonymous. Funding was not drug industry related. We  
16 declare that a similar paper is not in preparation, submitted, or under publication.  
17  
18

19 Data Sharing Statement: There is no additional data available.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1: Descriptive data on the participants

General information		Analgesics (49%)*			No Analgesics (51%)			Study population (100%)
		Female n=938 (%)#	Male n=993 (%)	All** n=1931 (%)	Female n=599 (%)	Male n=1,383 (%)	All** n=1,982 (%)	All n=3,913 (%)
Age	≤30 y	67 (7)	57 (6)	124 (6)	345 (58)	443 (32)	788 (40)	912 (23)
	>30, ≤50 y	724 (77)	789 (80)	1513 (78)	141 (24)	707 (51)	848 (43)	2361 (60)
	>50 y	147 (16)	147 (15)	294 (15)	113 (19)	233 (17)	346 (18)	640 (16)
	Mean (SD) y	42 (8·0)	43 (7·8)	43 (7·9)	34 (13·2)	38 (11·6)	37 (12·3)	40 (10·7)
Experience	amateur	916 (98)	980 (99)	1896 (98)	588 (98)	1,355 (98)	1943 (98)	3839 (98)
	professional	4 (<1)	2 (<1)	6 (<1)	6 (1)	17 (1)	23 (1)	29 (1)
Previous marathon experience	yes	927 (99)	974 (98)	1901 (98)	398 (66)	1,121 (81)	1,519 (77)	3420 (87)
Training per week last 3 months	<40 km	4 (<1)	4 (<1)	8 (<1)	345 (58)	286 (21)	631 (32)	639 (16)
	40-60 km	729 (78)	508 (51)	1237 (64)	135 (23)	769 (56)	904 (46)	2141 (55)
	>60 km	201 (21)	478 (48)	679 (35)	119 (20)	328 (24)	447 (23)	1126 (29)
	Mean (SD) km	55 (12·0)	61 (9·7)	58 (11·4)	40 (20·7)	53 (20·5)	49 (21·3)	53 (17·8)
Pain during training	yes	573 (61)	382 (39)	955 (50)	193 (32)	308 (22)	501 (25)	1456 (37)
Analgesic use during sport	yes	534 (57)	906 (91)	1440 (75)	33 (6)	189 (14)	222 (11)	1662 (43)
Analgesic use during training	yes	129 (14)	254 (26)	383 (20)	7 (1)	9 (1)	16 (1)	399 (10)
Pain immediately before the race	yes	160 (17)	48 (5)	208 (11)	9 (2)	13 (1)	22 (1)	230 (6)
Lab check <sup>1</sup>	yes	64 (7)	52 (5)	116 (6)	62 (10)	120 (9)	182 (9)	298 (8)

Information received on the risk of analgesics	yes	34 (4)	30 (3)	64 (3)	58 (10)	76 (6)	134 (7)	198 (5)
	no	889 (95)	936 (95)	1825 (95)	520 (87)	1273 (92)	1793 (91)	3618 (93)
Race entered	Marathon	147 (16)	434 (44)	581 (30)	48 (8)	355 (26)	355 (26)	984 (25)
	Half marathon	778 (83)	535 (54)	1313 (68)	545 (91)	1,010 (73)	1,010 (73)	2868 (73)
	Other/not stated	13	24	37	6	18	18	61 (2)
Adverse events	yes	133 (14)	179 (18)	312 (16)	40 (7)	32 (2)	32 (2)	384 (10)
	no							

\*Percentages relate to the primary study population, and rounded to the nearest whole number.

# Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

\*\*The difference of all parameters was significant ( $p=0.002$  to  $p<0.001$ ) when analgesic and control cohort were compared (chi square tests, Fishers tests and U-tests).

<sup>1</sup> Lab check; Laboratory parameters tested before the race (e.g. kidney values; see question 10 in figure 1)



Table 2: Use of analgesics before the marathon

Drugs	Doses	All n=1,931 (%) <sup>1</sup>	Female n=938 (%)	Male n=993 (%)
Diclofenac	≥ 100 mg (high)	219 (11)	91 (10)	128 (13)
	≤ 75 mg / unknown (low)	694 (36)	317 (34)	377 (38)
	None <sup>2</sup>	1,018	530	488
Ibuprofen	≥ 800 mg (high)	312 (16)	129 (14)	183 (18)
	≤ 600 mg / unknown (low)	410 (21)	217 (23)	193 (19)
	None	1,209	592	617
Aspirin	≥ 750 mg (high)	13 (<1)	8 (<1)	5 (<1)
	≤ 500 mg / unknown (low)	128 (7)	59 (6)	69 (7)
	None	1,790	871	919
Other analgesics <sup>3</sup>	High	68 (4)	44 (5)	24 (2)
	Low	107 (6)	70 (7)	37 (4)
	None	1,756	824	932
	Prescribed	42 (2)	21 (2)	21 (2)
	OTC	1,041 (54)	132 (14)	909 (92)
	Missing (data not reported)	848 (44)	785 (84)	63 (6)

<sup>1</sup> Percentages relate to the total number in the group, and rounded to the nearest whole number.

<sup>2</sup> The numbers in the 'no analgesic cohort', given for comparison.

<sup>3</sup> Other analgesics high dose / low dose, naproxen >500 mg / ≤ 500 mg or unknown, meloxicam ≥ 15 mg / ≤ 7.5 mg or unknown, celecoxib ≥ 400 mg / ≤ 200 mg or unknown, etoricoxib ≥ 120 mg / ≤ 90 mg or unknown, acetaminophen ≥ 1000 mg / ≤ 500 mg or unknown, dipyrrone ≥ 1000 mg / ≤ 500 mg or unknown.

Table 3: AE during and after the marathon

Problems	Analgesics (49%)				No Analgesics (51%)			
	Half marathon n=1,313 (%) <sup>1</sup>	Marathon n=581 (%)	Other /not stated n=37 (%)	all n=1,931 (%)	Half marathon n=1,555 (%)	Marathon n=403 (%)	Other /not stated n=24 (%)	all n=1,982 (%)
<b>AEs<sup>2</sup></b>								
Urine blood	23 (2)	41 (7)	5 (14)	69 (4)	0 (0)	0 (0)	0 (0)	0 (0)
GI-cramp	84 (6)	98 (17)	3 (8)	185 (10)	7 (1)	8 (2)	0 (0)	15 (<1)
GI-bleeding	22 (2)	46 (8)	6 (16)	74 (4)	0 (0)	3 (1)	0 (0)	3 (<1)
CV-during race	11 (1)	66 (11)	1 (3)	78 (4)	3 (<1)	1 (<1)	0 (0)	4 (<1)
CV-post race	47 (4)	112 (19)	11 (30)	170 (9)	49 (3)	8 (2)	1 (4)	58 (3)
Total (individuals) <sup>3</sup>	138 (11)	158 (27)	16 (44)	312 (16)	55 (4)	16 (4)	1 (4)	72 (4)
<b>Reasons for premature race withdrawal</b>								
Intestinal cramp	35 (3)	0 (0)	0 (0)	35 (2)	12 (1)	0 (0)	0 (0)	12 (1)
Pain	14 (1)	3 (1)	0 (0)	17 (1)	16 (1)	0 (0)	0 (0)	16 (1)
Muscle cramp	9 (1)	1 (<1)	1 (3)	11 (1)	47 (3)	3 (1)	0 (0)	50 (3)
Others	8 (1)	3 (1)	1 (3)	12 (1)	14 (1)	1 (<1)	0 (0)	15 (1)
Total (individuals) <sup>4</sup>	66 (5)	7 (1)	2 (5)	75 (4)	89 (6)	4 (1)	0 (0)	93 (5)
<b>Pain post exercise</b>								
Joint	119 (9)	290 (50)	14 (38)	423 (22)	179 (12)	143 (36)	5 (21)	327 (17)
Muscle	929 (71)	308 (53)	22 (59)	1,259 (65)	642 (41)	271 (67)	10 (42)	923 (47)
Total (individuals)	955 (73)	323 (56)	23 (62)	1,301 (67)	710 (46)	274 (68)	11 (46)	995 (50)

<sup>1</sup> Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

<sup>2</sup> The difference of the incidence of all AEs was highly significant ( $p < 0.001$ ) when the "all" groups were combined, details and significance ranges are given in figure 4

<sup>3</sup> Number of individuals reporting AEs (a single individual may report >1 AE)

<sup>4</sup> The difference of withdrawals comparing the analgesic and control cohort was not significant ( $p = 0.237$ )

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

Table 4: Incidence of AE in relation to the analgesic used

Adverse events	Diclofenac n=913		Ibuprofen n=722		Aspirin n=141		Other analgesics n=175	
	Low dose n=693 <sup>1</sup> (%)	High dose n=220 (%)	Low dose n=410 (%)	High dose n=312 (%)	Low dose n=102 (%)	High dose n=39 (%)	Low dose n=107 (%)	High dose n=68 (%)
Urine blood	6 (1)	5 (2)	5 (1)	45 (14)	7 (7)	19 (49)	1 (1)	1 (2)
GI-cramp	16 (2)	5 (2)	52 (13)	89 (29)	11 (11)	9 (23)	4 (4)	9 (13)
GI-bleeding	2 (<1)	8 (4)	13 (3)	39 (13)	9 (9)	19 (49)	1 (1)	2 (3)
CV – during race	2 (<1)	0 (0)	40 (10)	28 (9)	3 (3)	8 (21)	5 (5)	0 (0)
CV – post race	4 (1)	8 (4)	44 (11)	97 (31)	11 (11)	12 (31)	3 (3)	3 (4)
Total (individuals) <sup>2</sup>	25 (4)	22 (10)	56 (14)	163 (52)	25 (25)	34 (87)	11 (10)	12 (18)

<sup>1</sup> % relative to the size of the group. Percentages rounded to the nearest whole number.

<sup>2</sup> Number of individuals reporting AEs (a single individual may report >1 AE)

See Table 2 for definition of dose sizes

Table 5: Serious adverse events causing hospitalisation

No.	Drug (dose and time of intake)	Reason for intake	Patient (sex, age)	Symptoms (time after intake)	Diagnosis (means)	Therapy	Outcome
1	Ibuprofen (600 mg BS)	Fear of joint pain	Female, 38 years	Oliguria, dyspnoea	Haematuria, hyperkalaemia, proteinuria	Furosemide, fluid, electrolytes	Recovered
2	Ibuprofen (400 mg BS and 400 mg DR)	Unknown	Male, 47 years	Anuria, haematuria at day 2	Empty bladder	Furosemide	Recovered
3	Ibuprofen (600 mg BS)	Joint pain (former body-builder), impaired kidney function	Male, 57 years	Anuria, arrhythmia (RR 220/120 mmHg)	Anuria	Haemofiltration, electrolytes, furosemide for 10 days	Incompletely recovered
4	Aspirin (500 mg BS)	Dysmenorrhoea	Female, 28 years	Black stool at day 1	Bleeding gastric ulcer	Gastroscopic intervention, omeprazole	Recovered
5	Aspirin (500 mg BS)	Fear of joint pain	Male, 43 years	Vomiting (blood stained), GI-cramps at day 1, black stool	Toxic erosive gastritis	Omeprazole	Recovered
6	Aspirin (1000 mg BS)	Enhance performance	Male, 33 years	GI-cramps, vomiting (blood stained)	Haemorrhagic gastritis	Gastroscopy, pantozole	Recovered
7	Aspirin (1000 mg BS)	Joint pain	Male, 53 years	GI-cramps (evening), black stool	2 gastric ulcers	Gastroscopic intervention, omeprazole	Recovered
8	Aspirin (500 mg BS)	Foot pain	Male, 38 years (experienced in sports)	Chest pain during race	ECG: infarction (small)	No specific therapy	Recovered
9	Aspirin (100 mg; BS)	Fear of infarction	Male, 51 years (apparently healthy)	Chest pain	ECG, troponin test: (small) infarction	Intensive care, rehabilitation	Unknown

BS = before start of the race; DR = during race; ECG = electrocardiogram; RR = blood pressure

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

**Literature:**

1. Schwartz JG, Merkel-Kraus S, Duval S, et al. Does longterm endurance running enhance or inhibit coronary artery plaque formation? A prospective multidetector CTA study of men completing marathons for least 25 consecutive years. *J Am Coll Cardiol* 2010;**55**(10):61625-7.
2. Mühlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J* 2008;**29**(15):1903-10.
3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol* 2011;**31**(5):986-1000.
4. Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: A randomised comparison. *Lancet* 2006;**368**(9549):1771-81.
5. Brune K, Niederweis U, Krämer BK. Sport und schmerzmittel: Unheilige allianz zum schaden der niere. *Deutsches Ärzteblatt* 2008;**105**(37):A1894-900.
6. Tscholl P, Alonso JM, Dollé G, Junge A, Dvorak J. The use of drugs and nutritional supplements in top-level track and field athletes. *Am J Sports Med* 2010;**38**(1):133-40.
7. Tscholl P, Feddermann N, Junge A, Dvorak J. The use and abuse of painkillers in international soccer: Data from 6 FIFA tournaments for female and youth players. *Am J Sports Med* 2009;**37**(2):260-5.
8. Taioli E. Use of permitted drugs in Italian professional soccer players. *Br J Sports Med* 2007;**41**(7):439-41.
9. Alaranta A, Alaranta H, Heliövaara M, Airaksinen M, Helenius I. Ample use of physician-prescribed medications in Finnish elite athletes. *Int J Sports Med* 2006;**27**(11):919-25.
10. Da Silva ER, De Rose EH, Ribeiro JP, et al. Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007). *Br J Sports Med* 2011;**45**(2):91-4.
11. Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med* 2005;**352**(15):1550-6.
12. Wharam PC, Speedy DB, Noakes TD, Thompson JM, Reid SA, Holtzhausen LM. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc* 2006;**38**(4):618-22.
13. Halvorsen FA, Lyng J, Ritland S. Gastrointestinal bleeding in marathon runners. *Scand J Gastroenterol* 1986;**21**(4):493-7.
14. Irving RA, Noakes TD, Raine RI, van Zyl Smit R. Transient oliguria with renal tubular dysfunction after a 90 km running race. *Med Sci Sports Exerc* 1990;**22**(6):756-61.

15. Le Meur Y, Paraf F, Szelag JC, Aldigier JC, Leroux-Robert C. Acute renal failure in a marathon runner: role of glomerular bleeding in tubular injury. *Am J Med* 1998;**105**(3): 251-2.
16. Boulter J, Noakes TD, Hew-Butler T. Acute renal failure in four Comrades Marathon runners ingesting the same electrolyte supplement: Coincidence or causation? *S Afr Med J* 2011;**101**(12):876-8.
17. Doraiswamy PM, Hoffman BM. Fitness and the brain: Can a walk a day keep Alzheimer's away? *Sci Am* 2008.
18. Lippi G, Franchini M, Guidi GC, Kean WF. Non-steroidal anti-inflammatory drugs in athletes. *Br J Sports Med* 2006;**40**(8):661-2; discussion 662-3.
19. Kehl O, Jäger K, Münch R, et al. Mesenteric anemia as a cause of jogging anemia? *Schweiz Med Wochenschr Suppl* 1986;**116**(29):974-6.
20. Noakes TD, Sharwood K, Speedy D, et al. Three independent biological mechanisms cause exercise-associated hyponatremia: evidence from 2,135 weighed competitive athletic performances. *Proc Natl Acad Sci U S A* 2005;**102**(51):18550-5.
21. Pals KL, Chang RT, Ryan AJ, Gisolfi CV. Effect of running intensity on intestinal permeability. *J Appl Physiol* 1997;**82**(2):571-6.
22. Scott PA, Kingsley GH, Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: Meta-analyses of observational studies and randomised controlled trials. *Eur J Heart Fail* 2008;**10**(11):1102-7.
23. Nieman DC, Henson DA, Dumke CL, et al. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Brain Behav Immun* 2006;**20**(6):578-84.
24. Hasson SM, Daniels JC, Divine JG, et al. Effect of ibuprofen use on muscle soreness, damage, and performance: A preliminary investigation. *Med Sci Sports Exerc* 1993;**25**(1):9-17.
25. Tokmakidis SP, Kokkinidis EA, Smilios I, Douda H. The effects of ibuprofen on delayed muscle soreness and muscular performance after eccentric exercise. *J Strength Cond Res* 2003;**17**(1):53-9.
26. Donnelly AE, McCormick K, Maughan RJ, Whiting PH, Clarkson PM. Effects of a non-steroidal anti-inflammatory drug on delayed onset muscle soreness and indices of damage. *Br J Sports Med* 1988;**22**(1):35-8.
27. Lambert GP, Boylan M, Laventure JP, Bull A, Lanspa S. Effect of aspirin and ibuprofen on GI permeability during exercise. *Int J Sports Med* 2007;**28**(9):722-6.
28. Robertson JD, Maughan RJ, Davidson RJ. Faecal blood loss in response to exercise. *BMJ (Clin Res Ed)* 1987;**295**(6593):303-5.
29. Simons SM, Kennedy RG. Gastrointestinal problems in runners. *Curr Sports Med Rep* 2004;**3**(2):112-6.
30. Page AJ, Reid SA, Speedy DB, Mulligan GP, Thompson J. Exercise-associated hyponatremia, renal function, and nonsteroidal antiinflammatory drug use in an ultraendurance mountain run. *Clin J Sport Med* 2007;**17**(1):43-8.



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Bonn Marathon – Questionnaire for all sportsmen (2010)**

Participant number ..... (voluntary) to avoid double registration; anonymity assured!

1) Sex  female /  male

2)  non-professional or  professional athlete

3) Age (years) ..... J

4) Do have marathon experience?  yes /  no

5) Running performance/week within the last 3 months approximately .....km

6) Did you experience joint, muscle, or back pain during or after training?  yes /  no

7) Do you have experience with analgesics in connection with sport?  yes /  no

8) Did you ingest analgesics before today's marathon, such as diclofenac, aspirin, ibuprofen, naproxen, acetaminophen, dipyrone?

1. Did you take analgesics before the start?  yes /  no

2. Did you have pain before the start of today's marathon?  yes /  no

3. Which analgesic and which dose did you take?

Ibuprofen <input type="text" value="Please select..."/>	Diclofenac <input type="text" value="Please select..."/>	Aspirin <input type="text" value="Please select..."/>
Naproxen <input type="text" value="Please select..."/>	Meloxicam <input type="text" value="Please select..."/>	Celebrex <input type="text" value="Please select..."/>
Etoricoxib <input type="text" value="Please select..."/>	Acetaminophen <input type="text" value="Please select..."/>	Dipyrone <input type="text" value="Please select..."/>

Others: .....

4.  prescription or  OTC?

9) Do you use analgesic during training?  yes /  no

10) Did a physician check your laboratory values while preparing for the marathon (e.g. kidney lab values)?  yes /  no

11) Have you been informed about the risks of using analgesics in connection with a marathon?  yes /  no

12.) In which race did you participate:

a.  marathon,  half marathon,  relay (4 participants split the marathon distance)

b. Inline skating  full distance or  half distance

c. others: .....Km

13) During the race:

a. Hematuria  yes /  no

b. GI-cramps  yes /  no

c. GI-bleeds  yes /  no

d. CV-events (extrasystole, palpitation, tachycardia, and others)  yes /  no

14) After the race:

a. CV-events  yes /  no

b. Athralgia  yes /  no

c. Myalgia  yes /  no

15) I withdrew from the race for the following reason(s):

a.  I got tired of it

b.  I experienced severe pain

c.  I experienced GI-cramps

d.  I experienced muscle cramps

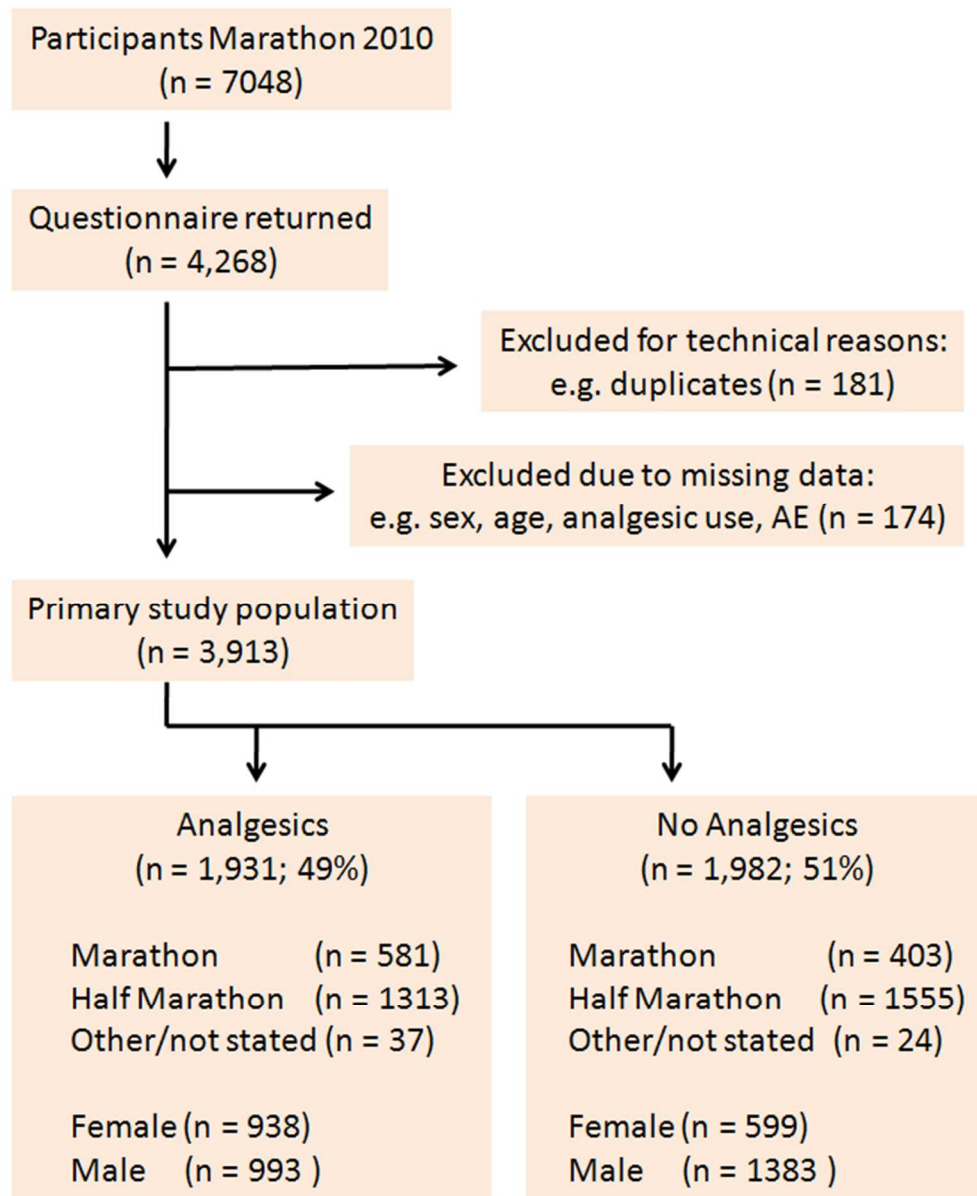
e.  other reasons: .....

Many thanks for your cooperation.

Dr. med. Michael Küster, Bonn, April 2010

Questionnaire supplied to marathon participants.  
103x68mm (300 x 300 DPI)

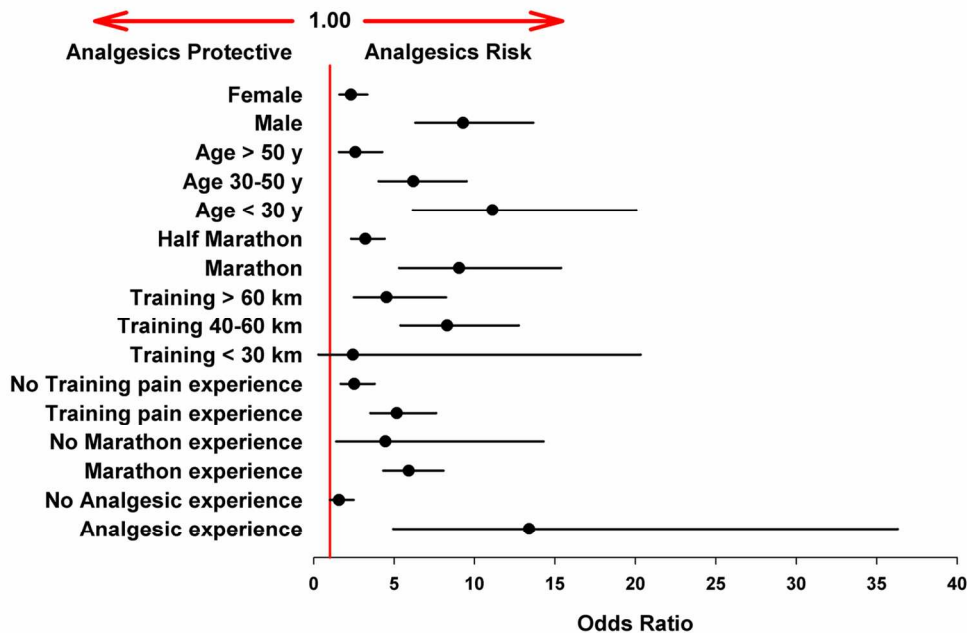
Review only



Flow chart of the evaluation of the marathon/half marathon running cohort. After the elimination of duplicates, almost 2,000 questionnaires were returned from each cohort. The distribution of marathon and half-marathon runners was similar in each treatment cohort. If participants entered races other than the marathon or half marathon (e.g. relays), or did not state which race they entered, they were captured in the 'other/not stated' cohort.

56x68mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

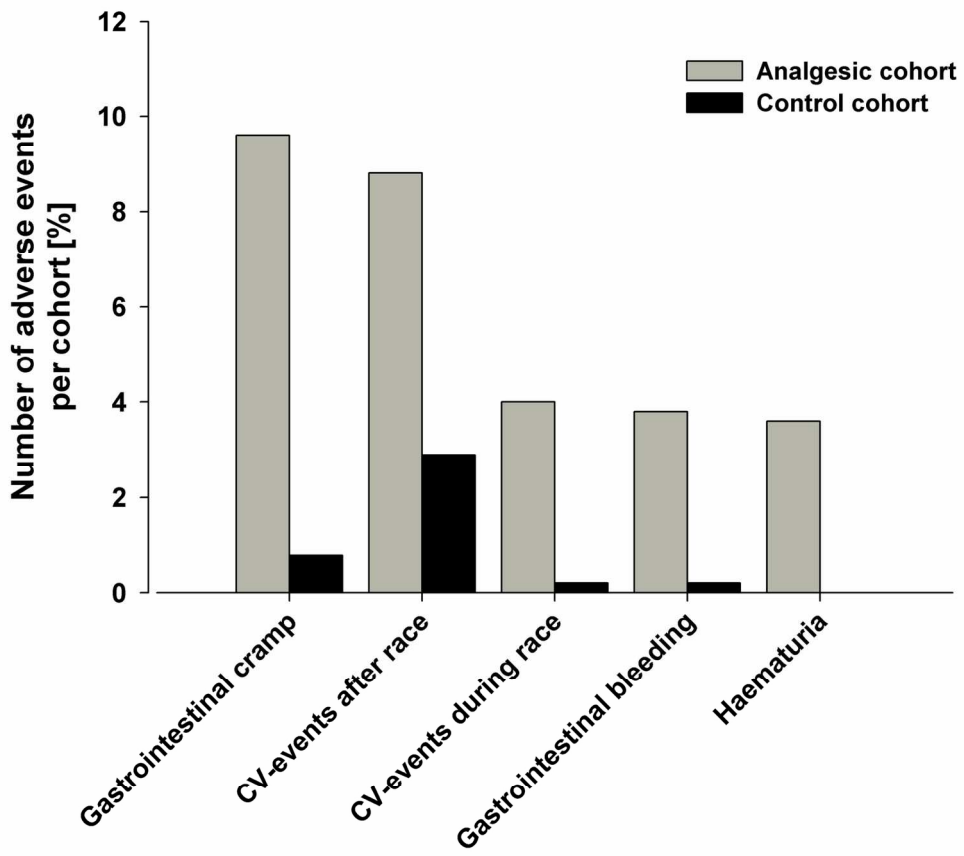


Risk of adverse events (AEs) within study subgroups (unadjusted). Odds ratios were estimated by binary linear regression analysis. Almost all subgroups show enhanced risk for AEs after analgesic use (odds ratios >1).

124x79mm (300 x 300 DPI)

view only

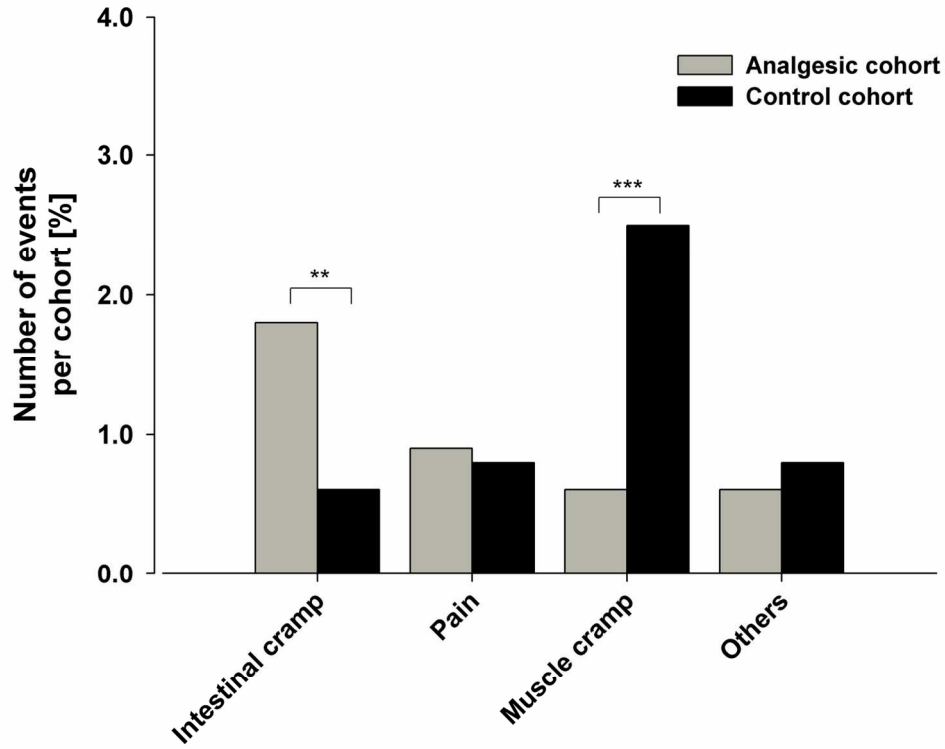
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Incidence of adverse events (AEs, derived from Table 3)  
 Rounded percentages are given in Table 3  
 The differences between the groups were all highly significant;  $p < 0.001$ .

150x144mm (300 x 300 DPI)





Reasons for premature termination of the race.

Rounded percentages are given in Table 3

\*\*p<0•01

\*\*\*p<0•001

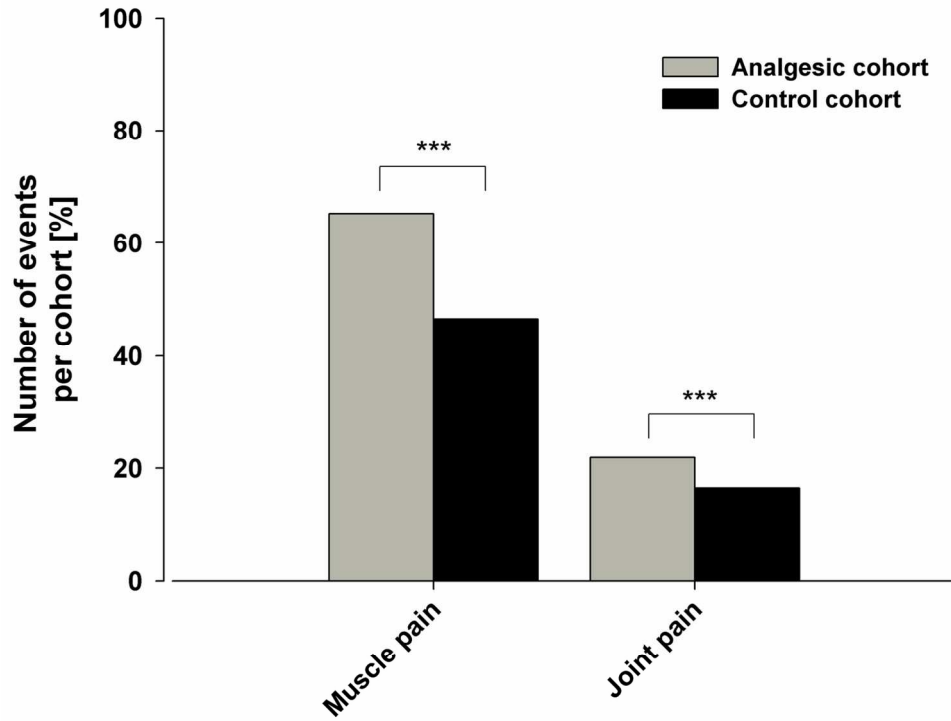
Note: the absolute numbers are small.

137x117mm (300 x 300 DPI)

Preprint

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

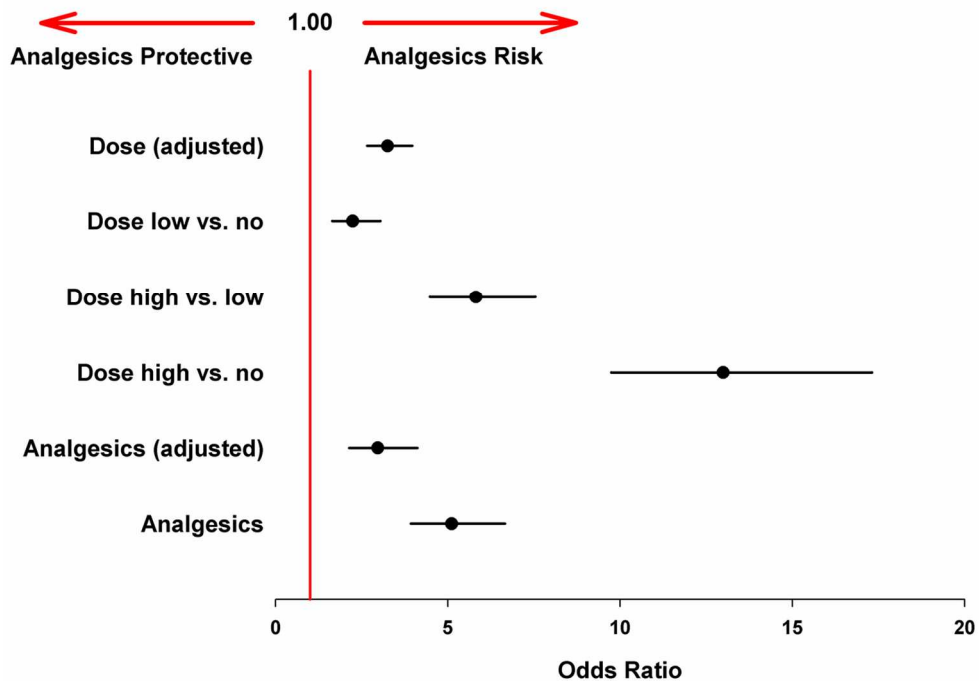
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



Percentage of runners experiencing muscle and/or joint pain after the race.  
Rounded percentages are given in Table 3  
The differences are highly significant (\*\*\*) p < 0.001).

131x108mm (300 x 300 DPI)

only



Adjusted risks for analgesic use and dose dependency  
There is a significant dose/AE relationship. Adjusted odds ratios were estimated by binary linear regression using possible confounders.

124x85mm (300 x 300 DPI)



**Consumption of analgesics before a marathon increases the incidence of cardiovascular, gastrointestinal, and renal problems in a dose-dependent manner**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002090.R1
Article Type:	Research
Date Submitted by the Author:	02-Dec-2012
Complete List of Authors:	Kuester, Michael; Schmerzzentrum DGS, Renner, Bertold; FAU Erlangen-Nuremberg, Department of Experimental and Clinical Pharmacology and Toxicology Oppel, Pascal; FAU Erlangen-Nuremberg, Niederweis, Ursula; Universtitaetsklinikum Erlangen, Anaesthesiologische Klinik Brune, Kay; FAU Erlangen-Nuremberg, Department of Experimental and Clinical Pharmacology and Toxicology
<b>Primary Subject Heading</b>:	Sports and exercise medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	PUBLIC HEALTH, SPORTS MEDICINE, Adverse events < THERAPEUTICS

SCHOLARONE™  
Manuscripts



1  
2  
3 **Consumption of analgesics before a marathon increases the incidence of**  
4 **cardiovascular, gastrointestinal, and renal problems in a dose-dependent**  
5 **manner**  
6  
7

8  
9  
10  
11 M. Küster<sup>#</sup>, B. Renner<sup>#</sup>, P. Oppel, U. Niederweis, K. Brune<sup>\*</sup>  
12  
13

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

\* Corresponding author

<sup>#</sup> Both authors contributed equally to the manuscript.

## Abstract

### Background

To prevent pain inhibiting their performance, many athletes ingest over-the-counter (OTC) analgesics before competing. The correlation between OTC analgesic use, dose, and adverse events (AEs) during and after racing has not been investigated to date.

### Methods

This prospective cohort study investigated the impact of analgesic use and dose on the incidence of AEs during the Bonn marathon/half marathon in 2010, using an on-line questionnaire which was available to all participating runners. Binary logistic regression models were used to calculate the risk of AEs associated with analgesic use and ingested doses, overall and by various subgroups.

### Findings

Of 7,048 participants, 3,913 responded to the questionnaires (the primary study population: 'respondents'). Of these, 49% ingested analgesics before the start of the marathon/half marathon ('analgesics cohort'). Diclofenac and ibuprofen were the main analgesics taken. There was no significant difference between premature race withdrawal rate in the analgesics cohort and the cohort who did not take analgesics ('controls'). However, race withdrawal because of gastrointestinal (GI) AEs was significantly more frequent in the analgesics cohort than in the control. Conversely, withdrawal because of muscle cramps was significantly more frequent in controls compared with the analgesics cohort. Furthermore, the analgesics cohort had an almost ten times higher incidence of AEs (overall risk difference 13%), and this incidence increased significantly with increasing analgesic dose. Nine respondents reported temporary hospitalisation: three for temporary kidney failure (post ibuprofen ingestion), four with bleeds (post aspirin ingestion), and two cardiac infarctions (post aspirin ingestion). None of the control reported hospitalisation.

### Interpretation

The use of analgesics before participating in endurance sports may cause many, potentially serious, unwanted AEs that increase with increasing analgesic dose; a

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

previously unrecognised medical problem. No reduction was seen in premature race withdrawal in the analgesics cohort compared with controls.

*Abstract word count = 291*

*Article word count = 3210*

*References count = 32*

For peer review only

## Introduction

Endurance sports are becoming increasingly popular. However, recent research has shown that physical activity does not automatically result in better health, but could exacerbate cardiovascular (CV) disease<sup>1,2</sup>. This may be related to the inhibition of cyclooxygenases by non-steroidal inflammatory drugs (NSAIDs), including 'over the counter' (OTC) analgesics, that are known to exacerbate atherosclerosis<sup>3</sup> and CV problems in some patients<sup>4</sup>.

Previous studies have shown that the use and abuse of analgesics in sports is frequent and possibly dangerous<sup>5-11</sup>, and that the incidence and severity of electrolyte disturbances<sup>12, 13</sup>, gastrointestinal (GI)<sup>14</sup>, and renal adverse events (AEs)<sup>15-17</sup> during and after racing double after taking analgesics. However, these studies investigated AEs in isolation and did not investigate a dose response relationship.

In a preliminary study, we interviewed 1,024 participants of the Bonn marathon/half marathon, and collected information on their training, fitness, and drug use<sup>5</sup>. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice<sup>5</sup>. These results were confirmed by Gorski et al<sup>18</sup>.

We now report a follow-up study aiming at defining the use of analgesics in relation to premature race withdrawal, and AEs occurring during and after racing.

## Methods

### Study population

The investigation relied on a questionnaire made available to all participants of the Bonn marathon/half marathon 2010 on paper and via the internet by the organizer together with information on the purpose of the investigation. Participating in the study was recommended by the organizer (Figure S1). The questionnaire examined:

1. Background epidemiology: age, sex, running experience, use of analgesics during training/in previous races, and details of previous training.
2. Medication use before the race: name and dose of drugs taken before the race start, and any medical advice received.

- 1  
2  
3 3. During and after racing: completion/reasons for premature withdrawal from the  
4 race, and AEs.  
5  
6

### 7 **Study design**

8  
9  
10 The study was conducted according to the Declaration of Helsinki on biomedical  
11 research involving human subjects (Somerset West amendment). Advertisement and  
12 study information was provided by the local organizer. All questionnaires returned  
13 were in an anonymised form which made identification of single participants  
14 impossible. The integrity of the participants remained unimpaired. After having  
15 consulted the local ethics committee, it was agreed that a formal application to the  
16 Institutional Ethics Review Board (IRB) was not required according to professional  
17 regulations. The scientific quality of the study design was not subjected to the control  
18 of the IRB.  
19

20  
21 The case reports (serious cases) were regarded as request for medical advice and  
22 handled as such by MK (MD) who preserved the anonymity of these “patients”.  
23  
24

25  
26 All data sheets (received questionnaires) were checked for completeness and  
27 duplicates using SPSS software version 19, followed by inspection by two  
28 researchers.  
29  
30

### 31 **Outcome measures**

32  
33 The primary hypothesis was that consumption of analgesics is associated with an  
34 increased incidence of AEs. An AE was included in the analysis if one or more of the  
35 following events were recorded on the questionnaire: GI cramps and bleeds,  
36 haematuria, or CV events (e.g. arrhythmia, palpitation).  
37  
38

### 39 **Statistical analysis**

40  
41 AEs and reasons for premature race withdrawal were tabulated according to a  
42 number of population-based factors which may influence drug use or AE incidence.  
43 Cross-tables, the chi square test, or Fisher’s test were used to analyse subgroups to  
44 establish relative risk differences and possible confounding factors. Drug doses (no  
45 drug, low dose, and high dose) were used to determine possible dose-related effects  
46 on AE incidence and race withdrawal.  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 A binary regression model was used to estimate odds ratios and 95% confidence  
4 intervals for AE incidence in subgroups and in the primary study population, with  
5 adjustment for confounding factors. Analyses were conducted using SPSS software  
6 version 19. Statistical tests were two-sided, and p-values less than 0.05 were  
7 considered statistically significant. AEs from respondents who did not state which  
8 race they entered were not included in the marathon/half marathon sub-group  
9 analysis.  
10  
11  
12  
13

### 14 **Results**

15  
16  
17 4,268 completed questionnaires were returned. More than 90% of the questionnaires  
18 were received by day 10, the rest within day seventeen after the race. Approximately  
19 4% were identified as duplicates, and were excluded from the analysis (Figure 1). An  
20 additional 4% of questionnaires were excluded because primary data were missing  
21 (i.e. age, sex, drug use, AEs).  
22  
23  
24  
25

26  
27 The remaining 3,913 completed questionnaires constituted the primary study  
28 population, representing 56% of the participants in the Bonn marathon/half marathon  
29 2010 (Figure 1). Nearly half of the study cohort used analgesic before the actual race  
30 ('analgesic cohort': n=1931, 49%) and 51% reported not to have used any analgesic  
31 ('control group': n=1982; Figure 1).  
32  
33  
34  
35

### 36 Background epidemiology

37  
38 Descriptive epidemiological data are given in Table S1 (supplementary information).  
39 Overall, there were more men than women (2,376 vs. 1,537), and men were slightly  
40 older on average (means  $\pm$ SD: 40  $\pm$ 10 vs. 39  $\pm$ 11 years). Males and females were  
41 younger in the control group (means  $\pm$ SD analgesic group: male 43  $\pm$ 8, female 42  $\pm$ 8  
42 years vs. control group: male 38  $\pm$ 12, female 34  $\pm$ 13 years). Most respondents had  
43 previous marathon experience (overall 87%). In the analgesics cohort, 20% had also  
44 taken analgesics during training (male 26% vs. female 14%), compared with 1% of  
45 the control group. Of the analgesics cohort, 11% recorded pain before the race  
46 (compared with 1% of controls), and 16% recorded AEs during/after racing  
47 (compared with 2% of controls).  
48  
49  
50  
51  
52  
53  
54

### 55 Medication use before racing

1  
2  
3 In total, 1,931 respondents ingested analgesics before racing, to retard or avoid pain  
4 during the races and thereafter. They used analgesics immediately before the race.  
5  
6 Most of the analgesics (54%) were taken without prescription (Table S2), and  
7  
8 significantly more women (61%) took analgesics than men (42%).  
9

10 The most frequently used analgesic was diclofenac, used by 47% of the analgesics  
11 cohort before the race (Table S2). Many athletes (11%) resorted to supra-OTC doses  
12 of diclofenac (over 100 mg). The second most commonly used analgesic was  
13 ibuprofen, and 43 % of those who took ibuprofen ingested  $\geq 800$  mg (twice as the  
14 recommended OTC single dose). Aspirin was used less frequently, and mostly at low  
15 therapeutic doses. Acetaminophen, celecoxib, dipyrrone, etoricoxib, meloxicam, and  
16 naproxen were also used, although these drugs were taken by comparatively few  
17 athletes and are grouped as 'other analgesics' in the analysis (Table S2).  
18  
19

20  
21  
22 Of all respondents, 93% declared that they were not informed about the risks of  
23 using analgesics in connection with sports endurance (Table S1).  
24  
25  
26

#### 27 28 Events during and after the race: 29

30  
31 The incidence of reported AEs was significantly higher in runners of the full marathon  
32 compared with the half-marathon (18% vs 7%;  $p < 0.001$ ). Additionally, the analgesic  
33 related AE risk in the full marathon cohort was significantly higher than in the half  
34 marathon cohort (odds 9.04; 95% CI 5.31-15.39 vs 3.20; CI 2.32-4.42. Figure 2).  
35  
36  
37

38 There were similar numbers of half marathon and marathon runners in the analgesics  
39 cohort compared with controls.  
40  
41

42 A four to ten times higher incidence of each type of AE was observed in the  
43 analgesics cohort compared with controls (overall incidence 16% vs 4%. Table S3,  
44 Figure 3), with a calculated risk difference of 13%. The difference in the incidence of  
45 AEs between the two cohorts was most prominent with respect to GI cramps and CV-  
46 events (after race). In the analgesics cohort, GI cramps were the most frequent AE  
47 (reported by 14% of the cohort), followed by CV AEs after the race (9%). In the  
48 controls, CV AEs after the race were the most frequently reported AE (3%, Table S3).  
49  
50 Notably, haematuria was reported only in the analgesics cohort. The differences in  
51 the incidence of all AEs were highly significant between the two groups ( $p < 0.001$ ,  
52 Table S3, Figure 3).  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 No significant difference was found between the analgesics cohort and controls in  
4 terms of premature race withdrawal overall (Table S3,  $p=0.237$ ). Race withdrawal  
5 because of muscle cramps occurred significantly more often in controls (3% vs 1%,  
6 Table S3, Figure 4,  $p<0.001$ ), but the absolute difference was small. Conversely,  
7 intestinal cramps were significantly more frequently blamed for race withdrawal in the  
8 analgesics cohort compared with controls (2% vs 1%;  $p<0.01$ , Table S3, Figure 4).  
9  
10

11  
12  
13  
14 Joint and muscle pain after the race were significantly more frequent in the  
15 analgesics cohort than in controls (1,301 vs 955 respondents,  $p<0.001$ , Table S3,  
16 Figure 5).  
17  
18

19  
20 The overall risk for analgesic related AEs was estimated at 5.1 (95% CI 3.9-6.7;  
21  $p<0.001$ , Figure 6), giving a 'number needed to harm' of eight treated participants. In  
22 a subsequent subgroup analysis for sex, age, training, marathon/half marathon run,  
23 and analgesic experience, an enhanced risks (odds ratio) for the different subgroups  
24 was detected, but this was very variable (1.6-13.4, Figure 2). Therefore, these  
25 subgroup parameters were included in a regression analysis which resulted in a  
26 comparable adjusted analgesic related risk of 3.0 (95% CI 2.1-4.1;  $p<0.001$ , Figure  
27 6).  
28  
29  
30  
31  
32

33  
34 To investigate if the incidence of AEs was dose-dependent, a risk estimation of the  
35 size of the dose was conducted. The high dose resulted in a significantly higher risk  
36 of AEs compared with the lower dose or controls. Even the low dose group presented  
37 a higher risk of AEs compared with controls (Figure 6). This further adjusted  
38 regression model showed a statistically significant increased risk at rising doses,  
39 meaning that increasing the dose can increase the risk of AEs by three times (odds  
40 ratio 3.2; 95% CI, 2.7-4.0,  $p<0.001$ , Figure 6).  
41  
42  
43  
44  
45

46 Finally, the association of analgesic use with distinct side effect profiles was  
47 analysed. The ingestion of all three drugs used most frequently (aspirin, diclofenac,  
48 and ibuprofen) was associated with AEs in a dose-dependent manner (Table 1).  
49 Overall, the incidence (defined as the percentage of respondents reporting AEs out  
50 of the total number of respondents taking a particular analgesic) was highest with  
51 aspirin, followed by ibuprofen, and lowest with diclofenac in both subgroups (high  
52 and low dose of analgesics. Table 1). At high doses, 10% of diclofenac users, 52% of  
53 ibuprofen users, and 87% of aspirin users experienced AEs (Table 1). Aspirin was  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 associated with relatively numerous GI or kidney bleeds, compared with the other  
4 analgesics.  
5

### 6 7 **Serious cases**

8  
9  
10 In addition to the evaluation by questionnaire, the participants of the Bonn  
11 marathon/half marathon 2010 were encouraged to report serious events which  
12 required hospitalisation during the 3 days following the race to the physician in  
13 charge, this evaluation (MK). Nine case reports of hospitalisation were received  
14 (Table S4 by MK), all of which concerned participants of the analgesics cohort. Three  
15 athletes (numbers 1-3, Table S4) reported anuria/oliguria which started the day after  
16 the race and lasted for up to three days. In two cases this AE resolved after a  
17 hyperuric period, and one respondent reported ongoing renal problems (haematuria  
18 for 2 days - number 3, Table 5). In all three cases, moderate doses of ibuprofen (2 x  
19 400 mg, 600 mg, and 600 mg) were taken before and during the race together with  
20 large amounts of fluid.  
21  
22

23  
24  
25 Four respondents (numbers 4-7, Table S4) reported hospitalisation because of GI-  
26 bleeding (black stools and vomiting blood). Gastroendoscopic evaluation revealed at  
27 least one bleeding ulcer in all four respondents. They were treated endoscopically  
28 and given proton pump inhibitors. All four respondents had ingested moderate  
29 amounts of aspirin (500-1,000 mg) before the race, and all were released after a few  
30 days without obvious sequelae.  
31  
32

33  
34  
35 Two more respondents (numbers 8 and 9, Table S4) were hospitalised after ingesting  
36 aspirin before the race. One took a 100 mg dose to prevent infarction, the other took  
37 500 mg because of mild foot pain. Both respondents complained of chest pain,  
38 angina, and arrhythmia the day after racing, and both suffered cardiac infarctions.  
39 Both athletes recovered, although some cardiac damage remained in one  
40 respondent.  
41  
42

43  
44  
45 These nine cases are well documented (Table S4). However, it should be noted that  
46 since reporting was spontaneous and voluntary, and a lack of corresponding  
47 hospitalisations in the control cohort could not be proven. Also we do not know if the  
48 patients/participants filled and submitted an (anonymized) questionnaire.  
49  
50

### 51 52 **Discussion**

1  
2  
3 It is known that many professional and amateur athletes use analgesics  
4 prophylactically to increase performance and prevent pain<sup>6-17, 19, 20</sup>.

5  
6  
7 A recent publication in the NEJM<sup>12</sup> warned that over-hydration during marathons  
8 might increase the risk of CV events. However, this study did not investigate the  
9 association between the use of drugs and CV problems. Recently, we reported that  
10 two-thirds of the participants of a marathon took analgesics before the start. This  
11 investigation showed that most athletes taking analgesics had taken supra-  
12 therapeutic doses. Similar data were reported by Gorski et al<sup>18</sup>. However, these  
13 studies did not investigate the use of analgesics and premature race withdrawal, nor  
14 did they systematically record performance and incidence of AEs.  
15  
16  
17  
18  
19

20  
21 The current study was designed to test the hypothesis that cyclooxygenase inhibitors  
22 contribute to the development of AEs, which is possible since these drugs block the  
23 protective effects of prostaglandins on GI, CV, and renal function. We hypothesise  
24 that their use is likely to suspend the mucosa- and kidney-protective<sup>3</sup> effects of  
25 PGE<sub>2</sub>/PGI<sub>2</sub>, thus augmenting the damaging effect of diminished blood flow<sup>21</sup> and  
26 oxygen supply for the GI mucosa and kidney<sup>22</sup>. Moreover, it was postulated that  
27 marathon runs could decrease the barrier function of the intestinal mucosa, further  
28 increasing the absorption of bacterial toxins from the gut<sup>23</sup>, and that repeated  
29 inhibition of the production of endothelium-produced PGI<sub>2</sub> during CV stress, e.g.  
30 intensive exercise, may accelerate atherosclerosis<sup>1, 2, 24</sup>.  
31  
32  
33  
34  
35  
36  
37

38  
39 This study analysed respondents for age, sex, training status, drug use (including  
40 doses), race completion, and AEs that occurred during the race and afterwards. To  
41 the best of our knowledge, this study shows for the first time that the administration of  
42 analgesics before a marathon/half-marathon can significantly increase AEs, and  
43 these increase with increasing analgesic dose. This increased incidence of AEs is  
44 dramatic; e.g. 4% of respondents in the analgesics cohort reported haematuria  
45 compared with 0% of controls. Moreover, nine respondents reported hospitalisation  
46 caused by either temporary kidney failure, bleeding ulcers, or cardiac infarctions. All  
47 these serious events occurred in the analgesics cohort.  
48  
49  
50  
51  
52

53  
54  
55 Altogether, these data do not support the contention that taking analgesics before  
56 racing improves the ability to complete the race or to prevent AEs thereafter.  
57

58  
59 Four aspects of this study deserve an in-depth discussion.  
60

1  
2  
3 1. *Analgesics taken prophylactically before racing do not prevent pain*  
4

5 Analysis of the pain reported by respondents before and after racing showed  
6 no major identifiable advantages gained from taking analgesics. Muscle  
7 cramps were reported as a reason for premature race withdrawal marginally  
8 less frequently in the analgesics cohort compared with the control. Although  
9 the difference was significant ( $p < 0.001$ ), the small sample size does not allow  
10 concrete conclusions to be drawn, particularly in the context of the parameters  
11 of overall pain during racing and intestinal cramps. There were significantly  
12 more intestinal cramps in the analgesics cohort ( $p < 0.001$ ) compared with the  
13 control, and more muscle and joint pain were reported in the analgesics cohort  
14 after racing than in the control.  
15  
16  
17  
18  
19  
20  
21

22 This result supports observations reported by Nieman *et al.*, who found that  
23 the intake of ibuprofen at regular intervals during an ultra-marathon race did  
24 not decrease muscle soreness in the days afterwards<sup>25</sup>. This may be  
25 explained by the fact that all the drugs investigated (diclofenac, ibuprofen, and  
26 aspirin) display a short elimination half-life of around two hours, which would  
27 make effects several hours after the ingestion of the drugs rather unlikely. In  
28 the report by Nieman *et al.*, the last dose of ibuprofen was taken several hours  
29 before finishing the race, and so the lack of influence on post-race pain is not  
30 surprising. Several research groups have reported the analgesic effects of  
31 NSAIDs in volunteers undertaking physical exercise. However, in these  
32 studies, the drugs were given after exercise, not before, which makes their  
33 reported analgesic effect plausible and recognisable<sup>26-28</sup>.  
34  
35  
36  
37  
38  
39  
40  
41  
42

43 In conclusion, our data indicate that the intake of cyclooxygenase inhibitor  
44 analgesics does not offer protection from pain during or after a marathon/half  
45 marathon compared with controls. However definitive proof of this contention  
46 would warrant a prospective, randomised cohort study.  
47  
48  
49  
50

51 2. *Analgesics contribute to AEs*  
52

53 This study investigated if cyclooxygenase inhibitors contribute to the AEs  
54 observed frequently in endurance sports<sup>23, 29</sup>. All of the AEs observed  
55 frequently during marathons, i.e. CV events, GI cramps/bleeds, and renal  
56 dysfunction, occurred much more frequently in the analgesics cohort  
57  
58  
59  
60

1  
2  
3 compared with the control. This effect was not dependent on the type of  
4 analgesic, i.e. all three drugs used frequently caused an increase in CV, GI,  
5 and renal AEs. This supports our hypothesis that the use of cyclooxygenase  
6 inhibitors before the start of a race may be damaging because tissue  
7 protection that is usually provided by prostaglandins may be impaired,  
8 triggering GI, CV, and renal AEs. These effects again suggest that the use of  
9 cyclooxygenase inhibitors before and during a marathon/half marathon race  
10 may be dangerous and should be avoided.

### 11 12 13 14 15 16 17 3. *The AE profile of different analgesics is different*

18  
19 Although the use of analgesics increases the overall incidence of AEs, all nine  
20 serious events reported to us which led to temporary hospitalisation concur  
21 with the pattern of AEs seen per drug in the rest of the respondents. The three  
22 temporary kidney failure cases (all of whom had ingested ibuprofen)  
23 correspond with the relatively high incidence of renal AEs in the ibuprofen  
24 group (Table 1). Moreover, the bleeding ulcers observed in the aspirin group  
25 mirror the high incidence of GI problems seen after the intake of aspirin.  
26 Somewhat surprising is the fact that both cardiac infarctions occurred in the  
27 aspirin group. This is interesting since aspirin should have protected from such  
28 events. However, definite conclusions cannot be drawn because of the small  
29 sample size. Overall, our observations are in line with previous reports<sup>1, 30-32</sup>.

### 30 31 32 33 34 35 36 37 38 4. *Limitations of the study*

39  
40 A double-blind, randomized, cross-over design for any trial is the gold  
41 standard. However, this is obviously impractical in these circumstances.  
42 Despite the relatively high return of questionnaires, there was still no  
43 information available for half of the marathon/half marathon participants, and  
44 many confounding factors such as BMI, use of other drugs etc. were not  
45 investigated. Although the two cohorts were of similar sizes, there are  
46 differences between them with respect to age, sex, training, and drug  
47 experience (a contribution of long term use of OTC analgesic on the incidence  
48 of AEs cannot be excluded), which may also have influenced the outcome.  
49 However, the considerable homogeneity of the AEs seen throughout all  
50 subgroups supports the overall contention that cyclooxygenase inhibitors  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 taken before and during a marathon/half marathon race increase the risks of  
4 AEs substantially, without measurable benefit in terms of race completion.  
5  
6

7 Taken together, our data indicate that the widespread use of cyclooxygenase  
8 inhibitors in connection with endurance sports is potentially damaging. In our study,  
9 the administration of analgesics before the start of a race did not prevent post-  
10 exercise pain or significantly reduce the premature withdrawal rate compared with the  
11 control. Conversely, the use of cyclooxygenase inhibitors considerably increased the  
12 incidence of GI, renal, and CV AEs. We conclude that the use of analgesics before  
13 and during endurance sports may pose a serious health problem that should be  
14 addressed. Our investigation has also shown a worrying lack of education about  
15 these AEs within the participants of the Bonn 2010 marathon/half marathon, which  
16 may highlight a larger problem if mirrored in the endurance sport community in  
17 general. We would encourage greater awareness of the possible AEs of these drugs,  
18 particularly among endurance sports enthusiasts.  
19  
20  
21  
22  
23  
24  
25  
26

27  
28 Further investigations are warranted to examine if the use of analgesics before and  
29 during sports activities should be avoided altogether.  
30  
31  
32  
33

### 34 **Acknowledgements**

35  
36  
37 K. Brune is Doerenkamp-Professor. He was supported by the Hertie Foundation.

38 The authors declare no conflict of interest.

39  
40 The authors acknowledge the assistance of a medical writer in the editing and  
41 language checking of this manuscript.  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1: Incidence of AE in relation to the analgesic used

Adverse events	Diclofenac n=913		Ibuprofen n=722		Aspirin n=141		Other analgesics n=175	
	Low dose n=693 <sup>1</sup> # of cases (%)	High dose n=220 # of cases (%)	Low dose n=410 # of cases (%)	High dose n=312 # of cases (%)	Low dose n=102 # of cases (%)	High dose n=39 # of cases (%)	Low dose n=107 # of cases (%)	High dose n=68 # of cases (%)
Urine blood	6 (1)	5 (2)	5 (1)	45 (14)	7 (7)	19 (49)	1 (1)	1 (2)
GI-cramp	16 (2)	5 (2)	52 (13)	89 (29)	11 (11)	9 (23)	4 (4)	9 (13)
GI-bleeding	2 (<1)	8 (4)	13 (3)	39 (13)	9 (9)	19 (49)	1 (1)	2 (3)
CV – during race	2 (<1)	0 (0)	40 (10)	28 (9)	3 (3)	8 (21)	5 (5)	0 (0)
CV – post race	4 (1)	8 (4)	44 (11)	97 (31)	11 (11)	12 (31)	3 (3)	3 (4)
Total (individuals) <sup>2</sup>	25 (4)	22 (10)	56 (14)	163 (52)	25 (25)	34 (87)	11 (10)	12 (18)

<sup>1</sup> % relative to the size of the group. Percentages rounded to the nearest whole number.

<sup>2</sup> Number of individuals reporting AEs (a single individual may report >1 AE)

See Table 2 for definition of dose sizes

**Literature:**

1. Schwartz JG, Merkel-Kraus, S., Duval, S., Harris, K., Peichel, G., Lesser, J.R., Knickelbine T., Flygenring, B., Longe, T.R., Pastorius, C., Roberts, W.R., Oesterle, S.C., Schwartz, R.S. Does longterm endurance running enhance or inhibit coronary artery plaque formation? A prospective multidetector CTA study of men completing marathons for least 25 consecutive years. *J Am Coll Cardiol.* 2010; **55**(10A): A.173.E1624.
2. Mohlenkamp S, Lehmann N, Breuckmann F, Brocker-Preuss M, Nassenstein K, Halle M, et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J.* 2008; **29**(15): 1903-10.
3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol.* 2011; **31**(5): 986-1000.
4. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet.* 2006; **368**(9549): 1771-81.
5. Brune K, Niederweis U, Krämer B. Sports and painkillers: Unholy alliance at the expense of renal failure. *Dtsch Arztebl* 2008; **105**(37): A 1894–7.
6. Tscholl P, Alonso JM, Dolle G, Junge A, Dvorak J. The use of drugs and nutritional supplements in top-level track and field athletes. *Am J Sports Med.* 2010; **38**(1): 133-40.
7. Tscholl P, Feddermann N, Junge A, Dvorak J. The use and abuse of painkillers in international soccer: data from 6 FIFA tournaments for female and youth players. *Am J Sports Med.* 2009; **37**(2): 260-5.
8. Tscholl PM, Dvorak J. Abuse of medication during international football competition in 2010 - lesson not learned. *Br J Sports Med.* 2012.
9. Taioli E. Use of permitted drugs in Italian professional soccer players. *Br J Sports Med.* 2007; **41**(7): 439-41.
10. Alaranta A, Alaranta H, Heliövaara M, Airaksinen M, Helenius I. Ample use of physician-prescribed medications in Finnish elite athletes. *Int J Sports Med.* 2006; **27**(11): 919-25.
11. Da Silva ER, De Rose EH, Ribeiro JP, Sampedro LB, Devos DV, Ferreira AO, et al. Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007). *Br J Sports Med.* 2011; **45**(2): 91-4.
12. Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med.* 2005; **352**(15): 1550-6.
13. Wharam PC, Speedy DB, Noakes TD, Thompson JM, Reid SA, Holtzhausen LM. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc.* 2006; **38**(4): 618-22.



14. Halvorsen FA, Lyng J, Ritland S. Gastrointestinal bleeding in marathon runners. *Scand J Gastroenterol.* 1986; **21**(4): 493-7.
15. Le Meur Y, Paraf F, Szelag JC, Aldigier JC, Leroux-Robert C. Acute renal failure in a marathon runner: role of glomerular bleeding in tubular injury. *Am J Med.* 1998; **105**(3): 251-2.
16. Irving RA, Noakes TD, Raine RI, Van Zyl Smit R. Transient oliguria with renal tubular dysfunction after a 90 km running race. *Med Sci Sports Exerc.* 1990; **22**(6): 756-61.
17. Boulter J, Noakes TD, Hew-Butler T. Acute renal failure in four Comrades Marathon runners ingesting the same electrolyte supplement: coincidence or causation? *S Afr Med J.* 2011; **101**(12): 876-8.
18. Gorski T, Cadore EL, Pinto SS, da Silva EM, Correa CS, Beltrami FG, et al. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med.* 2011; **45**(2): 85-90.
19. Doraiswamy PM, Hoffman B.M. Fitness and the Brain: Can a Walk a Day Keep Alzheimer's Away? *Scientific American.* 2008; **4**.
20. Lippi G, Franchini M, Guidi GC, Kean WF. Non-steroidal anti-inflammatory drugs in athletes. *Br J Sports Med.* 2006; **40**(8): 661-2; discussion 2-3.
21. Kehl O, Jager K, Munch R, Buhler H, Segantini P, Bollinger A, et al. [Mesenterial anemia as a cause of jogging anemia?]. *Schweiz Med Wochenschr.* 1986; **116**(29): 974-6.
22. Noakes TD, Sharwood K, Speedy D, Hew T, Reid S, Dugas J, et al. Three independent biological mechanisms cause exercise-associated hyponatremia: evidence from 2,135 weighed competitive athletic performances. *Proc Natl Acad Sci U S A.* 2005; **102**(51): 18550-5.
23. Pals KL, Chang RT, Ryan AJ, Gisolfi CV. Effect of running intensity on intestinal permeability. *J Appl Physiol.* 1997; **82**(2): 571-6.
24. Scott PA, Kingsley GH, Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. *Eur J Heart Fail.* 2008; **10**(11): 1102-7.
25. Nieman DC, Henson DA, Dumke CL, Oley K, McAnulty SR, Davis JM, et al. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Brain Behav Immun.* 2006; **20**(6): 578-84.
26. Tokmakidis SP, Kokkinidis EA, Smilios I, Douda H. The effects of ibuprofen on delayed muscle soreness and muscular performance after eccentric exercise. *J Strength Cond Res.* 2003; **17**(1): 53-9.
27. Hasson SM, Daniels JC, Divine JG, Niebuhr BR, Richmond S, Stein PG, et al. Effect of ibuprofen use on muscle soreness, damage, and performance: a preliminary investigation. *Med Sci Sports Exerc.* 1993; **25**(1): 9-17.
28. Donnelly AE, McCormick K, Maughan RJ, Whiting PH, Clarkson PM. Effects of a non-steroidal anti-inflammatory drug on delayed onset muscle soreness and indices of damage. *Br J Sports Med.* 1988; **22**(1): 35-8.
29. Lambert GP, Boylan M, Laventure JP, Bull A, Lanspa S. Effect of aspirin and ibuprofen on GI permeability during exercise. *Int J Sports Med.* 2007; **28**(9): 722-6.



- 1  
2  
3 30. Robertson JD, Maughan RJ, Davidson RJ. Faecal blood loss in response to  
4 exercise. Br Med J (Clin Res Ed). 1987; **295**(6593): 303-5.  
5  
6 31. Simons SM, Kennedy RG. Gastrointestinal problems in runners. Curr Sports  
7 Med Rep. 2004; **3**(2): 112-6.  
8  
9 32. Page AJ, Reid SA, Speedy DB, Mulligan GP, Thompson J. Exercise-  
10 associated hyponatremia, renal function, and nonsteroidal antiinflammatory drug use  
11 in an ultraendurance mountain run. Clin J Sport Med. 2007; **17**(1): 43-8.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 **Consumption of analgesics before a marathon increases the incidence of**  
4 **cardiovascular, gastrointestinal, and renal problems in a dose-dependent**  
5 **manner**  
6  
7

8  
9  
10  
11 M. Küster<sup>#</sup>, B. Renner<sup>#</sup>, P. Oppel, U. Niederweis, K. Brune<sup>\*</sup>  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

43 \* Corresponding author  
44

45 # Both authors contributed equally to the manuscript.  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Abstract

### Background

To prevent pain inhibiting their performance, many athletes ingest over-the-counter (OTC) analgesics before competing. The correlation between OTC analgesic use, dose, and adverse events (AEs) during and after racing has not been investigated to date.

### Methods

This prospective cohort study investigated the impact of analgesic use and dose on the incidence of AEs during the Bonn marathon/half marathon in 2010, using an on-line questionnaire which was available to all participating runners. Binary logistic regression models were used to calculate the risk of AEs associated with analgesic use and ingested doses, overall and by various subgroups.

### Findings

Of 7,048 participants, 3,913 responded to the questionnaires (the primary study population: 'respondents'). Of these, 49% ingested analgesics before the start of the marathon/half marathon ('analgesics cohort'). Diclofenac and ibuprofen were the main analgesics taken. There was no significant difference between premature race withdrawal rate in the analgesics cohort and the cohort who did not take analgesics ('controls'). However, race withdrawal because of gastrointestinal (GI) AEs was significantly more frequent in the analgesics cohort than in the control. Conversely, withdrawal because of muscle cramps was significantly more frequent in controls compared with the analgesics cohort. Furthermore, the analgesics cohort had an almost ten times higher incidence of AEs (overall risk difference 13%), and this incidence increased significantly with increasing analgesic dose. Nine respondents reported temporary hospitalisation: three for temporary kidney failure (post ibuprofen ingestion), four with bleeds (post aspirin ingestion), and two cardiac infarctions (post aspirin ingestion). None of the control reported hospitalisation.

### Interpretation

The use of analgesics before participating in endurance sports may cause many, potentially serious, unwanted AEs that increase with increasing analgesic dose; a

1  
2  
3 previously unrecognised medical problem. No reduction was seen in premature race  
4 withdrawal in the analgesics cohort compared with controls.  
5  
6  
7

8  
9 *Abstract word count = 291*  
10

11 *Article word count = 3210*  
12

13 *References count = 32*  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Introduction

Endurance sports are becoming increasingly popular. However, recent research has shown that physical activity does not automatically result in better health, but could exacerbate cardiovascular (CV) disease<sup>1,2</sup>. This may be related to the inhibition of cyclooxygenases by non-steroidal inflammatory drugs (NSAIDs), including 'over the counter' (OTC) analgesics, that are known to exacerbate atherosclerosis<sup>3</sup> and CV problems in some patients<sup>4</sup>.

Previous studies have shown that the use and abuse of analgesics in sports is frequent and possibly dangerous<sup>5-11</sup>, and that the incidence and severity of [CV<sup>11</sup>electrolyte disturbances](#)<sup>12, 13</sup>, gastrointestinal (GI)<sup>14</sup>, and renal adverse events (AEs)<sup>15-17</sup> during and after racing double after taking analgesics. However, these studies investigated AEs in isolation and did not investigate a dose response relationship.

In a preliminary study, we interviewed 1,024 participants of the Bonn marathon/half marathon, and collected information on their training, fitness, and drug use<sup>5</sup>. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice<sup>5</sup>. [These results were confirmed by Gorski et al<sup>18</sup>](#).

We now report a follow-up study [aiming at defining the use of analgesic and dose of analgesics](#) in relation to premature race withdrawal, and AEs occurring during and after racing.

## Methods

### Study population

The investigation relied on a questionnaire [made](#), available to all participants of the Bonn marathon/half marathon 2010 on paper and via the internet [by the organizer together with information on the purpose of the investigation. Participating in the study was recommended by the organizer](#) (Figure [S1](#)). The questionnaire examined:

1. Background epidemiology: age, sex, running experience, use of analgesics during training/in previous races, and details of previous training.

2. Medication use before the race: name and dose of drugs taken before the race start, and any medical advice received.
3. During and after racing: completion/reasons for premature withdrawal from the race, and AEs.

### Study design

The study was conducted according to the Declaration of Helsinki on biomedical research involving human subjects (Somerset West amendment). Advertisement and study information was provided by the local organizer. All questionnaires returned were in an anonymised form which made identification of single participants impossible. The integrity of the participants remained unimpaired. After having consulted the local ethics committee, it was agreed that a formal application to the Institutional Ethics Review Board (IRB) was not required according to professional regulations. The scientific quality of the study design was not subjected to the control of the IRB.

The case reports (serious cases) were regarded as request for medical advice and handled as such by MK (MD) who preserved the anonymity of these “patients”.

All data ~~sheets (received questionnaires) were submitted by internet or email, and~~ were checked for completeness and duplicates using SPSS software version 19, followed by inspection by two researchers.

### Outcome measures

The primary hypothesis was that consumption of analgesics is associated with an increased incidence of AEs. An AE was included in the analysis if one or more of the following events were recorded on the questionnaire: GI cramps and bleeds, haematuria, or CV events (e.g. arrhythmia, palpitation).

### Statistical analysis

AEs and reasons for premature race withdrawal were tabulated according to a number of population-based factors which may influence drug use or AE incidence. Cross-tables, the chi square test, or Fisher’s test were used to analyse subgroups to establish relative risk differences and possible confounding factors. Drug doses (no

1  
2  
3 drug, low dose, and high dose) were used to determine possible dose-related effects  
4 on AE incidence and race withdrawal.  
5

6  
7 A binary regression model was used to estimate odds ratios and 95% confidence  
8 intervals for AE incidence in subgroups and in the primary study population, with  
9 adjustment for confounding factors. Analyses were conducted using SPSS software  
10 version 19. Statistical tests were two-sided, and p-values less than 0.05 were  
11 considered statistically significant. AEs from respondents who did not state which  
12 race they entered were not included in the marathon/half marathon sub-group  
13 analysis.  
14  
15  
16  
17  
18

### 19 **Results**

20  
21 4,268 completed questionnaires were returned. [More than 90% of the questionnaires](#)  
22 [were received by day 10, the rest within day seventeen after the race.](#) Approximately  
23 4% were identified as duplicates, and were excluded from the analysis ([Figure 1](#)). An  
24 additional 4% of questionnaires were excluded because primary data were missing  
25 (i.e. age, sex, drug use, AEs).  
26  
27  
28  
29

30  
31 The remaining 3,913 completed questionnaires constituted the primary study  
32 population, representing 56% of the participants in the Bonn marathon/half marathon  
33 2010 ([Figure 21](#)). [Nearly half of the study cohort used analgesic before the actual](#)  
34 [race \('analgesic cohort': n=1931, 49%\) and 51% reported not to have used any](#)  
35 [analgesic \('control group': n=1982; \[Figure 1\]\(#\)\).](#)  
36  
37  
38  
39

#### 40 Background epidemiology

41  
42 Descriptive epidemiological data are given in Table [S1 \(supplementary information\)](#)  
43  
44 4. Overall, there were more men than women (2,376 vs. 1,537), and men were  
45 slightly older on average (~~means: 38 and 43 years vs. 34 and 42 years~~). (~~means~~  
46  ~~$\pm$ SD: 40  $\pm$ 10 vs. 39  $\pm$ 11 years~~). [Males and females were younger in the control group](#)  
47 [\(means  \$\pm\$ SD analgesic group: male 43  \$\pm\$ 8, female 42  \$\pm\$ 8 years vs. control group:](#)  
48 [male 38  \$\pm\$ 12, female 34  \$\pm\$ 13 years\).](#)  
49  
50  
51

52  
53 ~~A larger proportion of men used analgesics during training.~~ Most respondents (~~66-~~  
54 ~~99%~~) had previous marathon experience ([overall 87%](#)). In the ~~group who took~~  
55 ~~analgesics before or during the marathon/half marathon~~ ('analgesics cohort'), ~~14-26%~~  
56 [20%](#) had [also](#) taken analgesics during training ([male 26% vs. female 14%](#)),  
57  
58  
59  
60

1  
2  
3 compared with 1% of the [control](#) group ~~who did not take analgesics ('controls')~~. Of  
4 the analgesics cohort, ~~5-17~~ [only 11%](#) recorded pain before the race (compared with  
5 1-2% of controls), and ~~14-18~~ [16%](#) recorded AEs during/after racing (compared with 2-  
6 ~~7~~ % of controls).  
7  
8

#### 9 10 Medication use before racing

11  
12 In total, 1,931 respondents ingested analgesics before racing, to retard or avoid pain  
13 during the races and thereafter. ~~Nearly half of the respondents (49%)~~ [They](#) used  
14 analgesics immediately before the race, ~~m~~ Most of ~~which the analgesics~~ (54%) were  
15 taken without ~~medical~~ prescription (Table [S2](#)), and significantly more women ([61%](#))  
16 took analgesics than men (~~Table S1~~) ([42%](#)).  
17  
18

19  
20 The most frequently used analgesic was diclofenac, used by 47% of the analgesics  
21 cohort before the race (Table [S2](#)). Many athletes (11%) resorted to supra-OTC doses  
22 of diclofenac (over 100 mg). The second most commonly used analgesic was  
23 ibuprofen, and 43 % of those who took ibuprofen ingested  $\geq 800$  mg (twice as the  
24 recommended OTC single dose). Aspirin was used less frequently, and mostly at [low](#)  
25 therapeutic doses. Acetaminophen, celecoxib, dipyron, etoricoxib, meloxicam, and  
26 naproxen were also used, although these drugs were taken by comparatively few  
27 athletes and are grouped as 'other analgesics' in the analysis (Table [S2](#)).  
28  
29

30  
31 Of all respondents, 93% ~~had were declared that they were~~ not ~~been~~ informed about  
32 the risks of using analgesics in connection with sports [endurance](#) (Table [S1](#)).  
33  
34

#### 35 36 Events during and after the race:

37  
38 The incidence of [reported](#) AEs was significantly higher in runners of the full marathon  
39 compared with the half-marathon (18% vs 7%;  $p < 0.001$ ). Additionally, the analgesic  
40 related AE risk in the full marathon cohort was significantly higher than in the half  
41 marathon cohort (odds  $9.04$ ; 95% CI  $5.31-15.39$  vs  $3.20$ ; CI  $2.32-4.42$ . Figure [32](#)).  
42  
43

44  
45 There were similar numbers of half marathon and marathon runners in the analgesics  
46 cohort compared with controls.  
47  
48

49  
50 A four to ten times higher incidence of each type of AE was observed in the  
51 analgesics cohort compared with controls (overall incidence [16%](#) ~~4%~~ vs [4%](#) ~~16%~~.  
52 Table [S3](#), Figure [43](#)), with a calculated risk difference of 13%. The difference in the  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 incidence of AEs between the two cohorts was most prominent with respect to GI  
4 cramps and CV-events (after race). In the analgesics cohort, GI cramps were the  
5 most frequent AE (reported by 14% of the cohort), followed by ~~(unspecified)~~ CV AEs  
6 after the race (9%). In the controls, ~~(unspecified)~~ CV AEs after the race were the  
7 most frequently reported AE (3%, Table S3). Notably, haematuria ~~occurred was~~  
8 reported only in the analgesics cohort. The differences in the incidence of all AEs  
9 were highly significant between the two groups ( $p < 0.001$ , Table S3, Figure 43).

10  
11  
12  
13  
14  
15 No significant difference was found between the analgesics cohort and controls in  
16 terms of premature race withdrawal overall (Table S3,  $p = 0.237$ ). Race withdrawal  
17 because of muscle cramps occurred significantly more often in controls (3% vs 1%,  
18 Table S3, Figure 54,  $p < 0.001$ ), but the absolute difference was small. Conversely,  
19 intestinal cramps were significantly more frequently blamed for race withdrawal in the  
20 analgesics cohort compared with controls (2% vs 1%;  $p < 0.01$ , Table S3, Figure 54).

21  
22  
23  
24  
25  
26 Joint and muscle pain after the race were significantly more frequent in the  
27 analgesics cohort than in controls (1,301 vs 955 respondents,  $p < 0.001$ , Table S3,  
28 Figure 65).

29  
30  
31  
32 The overall risk for analgesic related AEs was estimated at 5.1 (95% CI 3.9-6.7;  
33  $p < 0.001$ , Figure 76), giving a 'number needed to harm' of eight treated  
34 peopleparticipants. In a subsequent subgroup analysis for sex, age, training,  
35 marathon/half marathon run, and analgesic experience, an enhanced risks (odds  
36 ratio) for the different subgroups was detected, but this was very variable (1.6-13.4,  
37 Figure 32). Therefore, these subgroup parameters were included in a regression  
38 analysis which resulted in a comparable adjusted analgesic related risk of 3.0 (95%  
39 CI 2.1-4.1;  $p < 0.001$ , Figure 76).

40  
41  
42  
43  
44  
45  
46 To investigate if the incidence of AEs was dose-dependent, a risk estimation of the  
47 size of the dose was conducted. The high dose resulted in a significantly higher risk  
48 of AEs compared with the lower dose or controls. Even the low dose group presented  
49 a higher risk of AEs compared with controls (Figure 76). This further adjusted  
50 regression model showed a statistically significant increased risk at rising doses,  
51 meaning that increasing the dose can increase the risk of AEs by three times (odds  
52 ratio 3.2; 95% CI, 2.7-4.0,  $p < 0.001$ , Figure 76).

1  
2  
3 Finally, the association of analgesic use with distinct side effect profiles was  
4 analysed. The ingestion of all three drugs used most frequently (aspirin, diclofenac,  
5 and ibuprofen) was associated with AEs in a dose-dependent manner (Table 41).  
6 Overall, the incidence (defined as the percentage of respondents reporting AEs out  
7 of the total number of respondents taking a particular analgesic) was highest with  
8 aspirin, followed by ibuprofen, and lowest with diclofenac in both subgroups (high  
9 and low dose of analgesics. Table 41). At high doses, 10% of diclofenac users, 52%  
10 of ibuprofen users, and 87% of aspirin users experienced AEs (Table 41). Aspirin  
11 was associated with relatively numerous GI or kidney bleeds, compared with the  
12 other analgesics.  
13  
14  
15  
16  
17  
18  
19

### 20 **Serious cases**

21  
22 In addition to the evaluation by questionnaire, the participants of the Bonn  
23 marathon/half marathon 2010 were asked encouraged to report serious events which  
24 required hospitalisation during the 3 days following the race. To to the physician in  
25 charge, this evaluation (MK)---. Nine case reports of hospitalisation were received  
26 (Table S45 by MK), all of which concerned respondents-participants of from the  
27 analgesics cohort. Three athletes (numbers 1-3, Table 5S4) reported anuria/oliguria  
28 which started the day after the race and lasted for up to three days. In two cases this  
29 AE resolved after a hyperuric period, and one respondent reported ongoing renal  
30 problems (haematuria for 2 days - number 3, Table 5). In all three cases, moderate  
31 doses of ibuprofen (2 x 400 mg, 600 mg, and 600 mg) were taken before and during  
32 the race together with large amounts of fluid.  
33  
34  
35  
36  
37  
38  
39  
40  
41

42 Four respondents (numbers 4-7, Table 5S4) reported hospitalisation because of GI-  
43 bleeding (black stools and vomiting blood). Gastroendoscopic evaluation revealed at  
44 least one bleeding ulcer in all four respondents. They were treated endoscopically  
45 and given proton pump inhibitors. All four respondents had ingested moderate  
46 amounts of aspirin (500-1,000 mg) before the race, and all were released after a few  
47 days without obvious sequelae.  
48  
49  
50  
51

52 Two more respondents (numbers 8 and 9, Table 5S4) were hospitalised after  
53 ingesting aspirin before the race. One took a 100 mg dose to prevent infarction, the  
54 other took 500 mg because of mild foot pain. Both respondents complained of chest  
55 pain, angina, and arrhythmia the day after racing, and both suffered cardiac  
56  
57  
58  
59  
60

1  
2  
3 infarctions. Both athletes recovered, although some cardiac damage remained in one  
4 respondent.

7 These nine cases are well documented (Table 5S4). However, it should be noted that  
8 since reporting was spontaneous and voluntary, and a lack of corresponding  
9 hospitalisations in the control cohort could not be proven. Also we do not know if the  
10 patients/participants filled and submitted an (anonymized) questionnaire.

### 14 **Discussion**

17 It is known that many professional and amateur athletes use analgesics  
18 prophylactically to increase performance and prevent pain<sup>6-17, 19, 20</sup>.

21 A recent publication in the NEJM<sup>12</sup> warned that over-hydration during marathons  
22 might increase the risk of CV events. However, this study did not investigate the  
23 association between the use of drugs and CV problems. Recently, we reported that  
24 two-thirds of the participants of a marathon took analgesics before the start. This  
25 investigation showed that most athletes taking analgesics had ~~either taken~~ **unsuitable**  
26 ~~drugs or~~ supra-therapeutic doses. Similar data were reported by Gorski et al<sup>18</sup>.

29 However, ~~these~~ **studies** did not investigate the use of analgesics and premature  
30 race withdrawal, nor did ~~it~~ **they** systematically record performance and incidence of  
31 AEs.

34 The current study was designed to test the hypothesis that cyclooxygenase inhibitors  
35 contribute to the development of AEs, which is possible since these drugs block the  
36 protective effects of prostaglandins on GI, CV, and renal function. We hypothesise  
37 that their use is likely to suspend the mucosa- and kidney-protective<sup>3</sup> effects of  
38 PGE<sub>2</sub>/PGI<sub>2</sub>, thus augmenting the damaging effect of diminished blood flow<sup>21</sup> and  
39 oxygen supply for the GI mucosa and kidney<sup>22</sup>. Moreover, it was postulated that  
40 marathon runs could decrease the barrier function of the intestinal mucosa, further  
41 increasing the absorption of bacterial toxins from the gut<sup>23</sup>, and that repeated  
42 inhibition of the production of endothelium-produced PGI<sub>2</sub> during CV stress, e.g.  
43 intensive exercise, may accelerate atherosclerosis<sup>1, 2, 24</sup>.

46 This study analysed respondents for age, sex, training status, drug use (including  
47 doses), race completion, and AEs that occurred during the race and afterwards. To  
48 the best of our knowledge, this study shows for the first time that the administration of  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 analgesics before a marathon/half-marathon can significantly increase AEs, and  
4 these increase with increasing analgesic dose. This increased incidence of AEs is  
5 dramatic; e.g. 4% of respondents in the analgesics cohort reported haematuria  
6 compared with 0% of controls. Moreover, nine respondents reported hospitalisation  
7 caused by either temporary kidney failure, bleeding ulcers, or cardiac infarctions. All  
8 these serious events occurred in the analgesics cohort.  
9  
10

11  
12  
13 Altogether, these data do not support the contention that taking analgesics before  
14 racing improves the ability to complete the race or to prevent AEs thereafter.  
15  
16

17  
18 Four aspects of this study deserve an in-depth discussion.  
19

20  
21 1. *Analgesics taken prophylactically before racing do not prevent pain*  
22

23 Analysis of the pain reported by respondents before and after racing showed  
24 no major identifiable advantages gained from taking analgesics. Muscle  
25 cramps were reported as a reason for premature race withdrawal marginally  
26 less frequently in the analgesics cohort compared with the control. Although  
27 the difference was significant ( $p < 0.001$ ), the small sample size does not allow  
28 concrete conclusions to be drawn, particularly in the context of the parameters  
29 of overall pain during racing and intestinal cramps. There were significantly  
30 more intestinal cramps in the analgesics cohort ( $p < 0.001$ ) compared with the  
31 control, and more muscle and joint pain were reported in the analgesics cohort  
32 after racing than in the control.  
33  
34  
35  
36  
37  
38

39  
40 This result supports observations reported by Nieman *et al.*, who found that  
41 the intake of ibuprofen at regular intervals during an ultra-marathon race did  
42 not decrease muscle soreness in the days afterwards<sup>25</sup>. This may be  
43 explained by the fact that all the drugs investigated (diclofenac, ibuprofen, and  
44 aspirin) display a short elimination half-life of around two hours, which would  
45 make effects several hours after the ingestion of the drugs rather unlikely. In  
46 the report by Nieman *et al.*, the last dose of ibuprofen was taken a few several  
47 hours before finishing the race, and so the lack of influence on post-race pain  
48 is not surprising. Several research groups have reported the analgesic effects  
49 of NSAIDs in volunteers undertaking physical exercise. However, in these  
50 studies, the drugs were given after exercise, not before, which makes their  
51 reported analgesic effect plausible and recognisable<sup>26-28</sup>.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 In conclusion, our data indicate that the intake of cyclooxygenase inhibitor  
4 analgesics does not offer protection from pain during or after a marathon/half  
5 marathon compared with controls. However definitive proof of this contention  
6 would warrant a prospective, randomised cohort study.  
7  
8  
9

## 10 2. *Analgesics contribute to AEs*

11  
12 This study investigated if cyclooxygenase inhibitors contribute to the AEs  
13 observed frequently in endurance sports<sup>23, 29</sup>. All of the AEs observed  
14 frequently during marathons, i.e. CV events, GI cramps/bleeds, and renal  
15 dysfunction, occurred much more frequently in the analgesics cohort  
16 compared with the control. This effect was not dependent on the type of  
17 analgesic, i.e. all three drugs used frequently caused an increase in CV, GI,  
18 and renal AEs. This supports our hypothesis that the use of cyclooxygenase  
19 inhibitors before the start of a race may be damaging because tissue  
20 protection that is usually provided by prostaglandins may be impaired,  
21 triggering GI, CV, and renal AEs. These effects again suggest that the use of  
22 cyclooxygenase inhibitors before and during a marathon/half marathon race  
23 may be dangerous and should be avoided.  
24  
25  
26  
27  
28  
29  
30  
31  
32

## 33 3. *The AE profile of different analgesics is different*

34  
35 Although the use of analgesics increases the overall incidence of AEs, all nine  
36 serious events reported to us which led to temporary hospitalisation concur  
37 with the pattern of AEs seen per drug in the rest of the respondents. The three  
38 temporary kidney failure cases (all of whom had ingested ibuprofen)  
39 correspond with the relatively high incidence of renal AEs in the ibuprofen  
40 group (Table 5, Table 41). Moreover, the bleeding ulcers observed in the  
41 aspirin group mirror the high incidence of GI problems seen after the intake of  
42 aspirin. Somewhat surprising is the fact that both cardiac infarctions occurred  
43 in the aspirin group. This is interesting since aspirin should have protected  
44 from such events. However, definite conclusions cannot be drawn because of  
45 the small sample size. Overall, our observations are in line with previous  
46 reports<sup>1, 30-32</sup>.  
47  
48  
49  
50  
51  
52  
53  
54  
55

## 56 4. *Limitations of the study*

1  
2  
3 A double-blind, randomized, cross-over design for any trial is the gold  
4 standard. However, this is obviously impractical in these circumstances.  
5  
6 Despite the relatively high return of questionnaires, there was still no  
7  
8 information available for half of the marathon/half marathon participants, and  
9  
10 many confounding factors such as BMI, use of other drugs etc. were not  
11  
12 investigated. Although the two cohorts were of similar sizes, there are  
13  
14 differences between them with respect to age, sex, training, and drug  
15  
16 experience (a contribution of long term use of OTC analgesic on the incidence  
17  
18 of AEs cannot be excluded), which may also have influenced the outcome.  
19  
20 However, the considerable homogeneity of the AEs seen throughout all  
21  
22 subgroups supports the overall contention that cyclooxygenase inhibitors  
23  
24 taken before and during a marathon/half marathon race increase the risks of  
25  
26 AEs substantially, without measurable benefit in terms of race completion.

25  
26 Taken together, our data indicate that the widespread use of cyclooxygenase  
27  
28 inhibitors in connection with endurance sports is potentially damaging. In our study,  
29  
30 the administration of analgesics before the start of a race did not prevent post-  
31  
32 exercise pain or significantly reduce the premature withdrawal rate compared with the  
33  
34 control. Conversely, the use of cyclooxygenase inhibitors considerably increased the  
35  
36 incidence of GI, renal, and CV AEs. We conclude that the use of analgesics before  
37  
38 and during endurance sports may pose a serious health problem that should be  
39  
40 addressed. Our investigation has also shown a worrying lack of education about  
41  
42 these AEs within the participants of the Bonn 2010 marathon/half marathon, which  
43  
44 may highlight a larger problem if mirrored in the endurance sport community in  
45  
46 general. We would encourage greater awareness of the possible AEs of these drugs,  
47  
48 particularly among endurance sports enthusiasts.

46  
47 Further investigations are warranted to examine if the use of analgesics before and  
48  
49 during sports activities should be avoided altogether.

## 52 53 **Acknowledgements**

54  
55 K. Brune is Doerenkamp-Professor. He was supported by the Hertie Foundation.  
56  
57 The authors declare no conflict of interest.  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

The authors acknowledge the assistance of a medical writer in the editing and language checking of this manuscript.

For peer review only

Table 41: Incidence of AE in relation to the analgesic used

Adverse events	Diclofenac n=913		Ibuprofen n=722		Aspirin n=141		Other analgesics n=175	
	Low dose n=693 <sup>1</sup> # of cases (%)	High dose n=220 # of cases (%)	Low dose n=410 # of cases (%)	High dose n=312 # of cases (%)	Low dose n=102 # of cases (%)	High dose n=39 # of cases (%)	Low dose n=107 # of cases (%)	High dose n=68 # of cases (%)
Urine blood	6 (1)	5 (2)	5 (1)	45 (14)	7 (7)	19 (49)	1 (1)	1 (2)
GI-cramp	16 (2)	5 (2)	52 (13)	89 (29)	11 (11)	9 (23)	4 (4)	9 (13)
GI-bleeding	2 (<1)	8 (4)	13 (3)	39 (13)	9 (9)	19 (49)	1 (1)	2 (3)
CV – during race	2 (<1)	0 (0)	40 (10)	28 (9)	3 (3)	8 (21)	5 (5)	0 (0)
CV – post race	4 (1)	8 (4)	44 (11)	97 (31)	11 (11)	12 (31)	3 (3)	3 (4)
Total (individuals) <sup>2</sup>	25 (4)	22 (10)	56 (14)	163 (52)	25 (25)	34 (87)	11 (10)	12 (18)

<sup>1</sup> % relative to the size of the group. Percentages rounded to the nearest whole number.

<sup>2</sup> Number of individuals reporting AEs (a single individual may report >1 AE)

See Table 2 for definition of dose sizes



**Literature:**

1. Schwartz JG, Merkel-Kraus, S., Duval, S., Harris, K., Peichel, G., Lesser, J.R., Knickelbine T., Flygenring, B., Longe, T.R., Pastorius, C., Roberts, W.R., Oesterle, S.C., Schwartz, R.S. Does longterm endurance running enhance or inhibit coronary artery plaque formation? A prospective multidetector CTA study of men completing marathons for least 25 consecutive years. *J Am Coll Cardiol.* 2010; **55**(10A): A.173.E1624.
2. Mohlenkamp S, Lehmann N, Breuckmann F, Brocker-Preuss M, Nassenstein K, Halle M, et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J.* 2008; **29**(15): 1903-10.
3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol.* 2011; **31**(5): 986-1000.
4. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet.* 2006; **368**(9549): 1771-81.
5. Brune K, Niederweis U, Krämer B. Sports and painkillers: Unholy alliance at the expense of renal failure. *Dtsch Arztebl* 2008; **105**(37): A 1894–7.
6. Tscholl P, Alonso JM, Dolle G, Junge A, Dvorak J. The use of drugs and nutritional supplements in top-level track and field athletes. *Am J Sports Med.* 2010; **38**(1): 133-40.
7. Tscholl P, Feddermann N, Junge A, Dvorak J. The use and abuse of painkillers in international soccer: data from 6 FIFA tournaments for female and youth players. *Am J Sports Med.* 2009; **37**(2): 260-5.
8. Tscholl PM, Dvorak J. Abuse of medication during international football competition in 2010 - lesson not learned. *Br J Sports Med.* 2012.
9. Taioli E. Use of permitted drugs in Italian professional soccer players. *Br J Sports Med.* 2007; **41**(7): 439-41.
10. Alaranta A, Alaranta H, Heliövaara M, Airaksinen M, Helenius I. Ample use of physician-prescribed medications in Finnish elite athletes. *Int J Sports Med.* 2006; **27**(11): 919-25.
11. Da Silva ER, De Rose EH, Ribeiro JP, Sampedro LB, Devos DV, Ferreira AO, et al. Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007). *Br J Sports Med.* 2011; **45**(2): 91-4.
12. Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med.* 2005; **352**(15): 1550-6.
13. Wharam PC, Speedy DB, Noakes TD, Thompson JM, Reid SA, Holtzhausen LM. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc.* 2006; **38**(4): 618-22.

14. Halvorsen FA, Lyng J, Ritland S. Gastrointestinal bleeding in marathon runners. *Scand J Gastroenterol.* 1986; **21**(4): 493-7.
15. Le Meur Y, Paraf F, Szelag JC, Aldigier JC, Leroux-Robert C. Acute renal failure in a marathon runner: role of glomerular bleeding in tubular injury. *Am J Med.* 1998; **105**(3): 251-2.
16. Irving RA, Noakes TD, Raine RI, Van Zyl Smit R. Transient oliguria with renal tubular dysfunction after a 90 km running race. *Med Sci Sports Exerc.* 1990; **22**(6): 756-61.
17. Boulter J, Noakes TD, Hew-Butler T. Acute renal failure in four Comrades Marathon runners ingesting the same electrolyte supplement: coincidence or causation? *S Afr Med J.* 2011; **101**(12): 876-8.
18. Gorski T, Cadore EL, Pinto SS, da Silva EM, Correa CS, Beltrami FG, et al. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med.* 2011; **45**(2): 85-90.
19. Doraiswamy PM, Hoffman B.M. Fitness and the Brain: Can a Walk a Day Keep Alzheimer's Away? *Scientific American.* 2008; **4**.
20. Lippi G, Franchini M, Guidi GC, Kean WF. Non-steroidal anti-inflammatory drugs in athletes. *Br J Sports Med.* 2006; **40**(8): 661-2; discussion 2-3.
21. Kehl O, Jager K, Munch R, Buhler H, Segantini P, Bollinger A, et al. [Mesenterial anemia as a cause of jogging anemia?]. *Schweiz Med Wochenschr.* 1986; **116**(29): 974-6.
22. Noakes TD, Sharwood K, Speedy D, Hew T, Reid S, Dugas J, et al. Three independent biological mechanisms cause exercise-associated hyponatremia: evidence from 2,135 weighed competitive athletic performances. *Proc Natl Acad Sci U S A.* 2005; **102**(51): 18550-5.
23. Pals KL, Chang RT, Ryan AJ, Gisolfi CV. Effect of running intensity on intestinal permeability. *J Appl Physiol.* 1997; **82**(2): 571-6.
24. Scott PA, Kingsley GH, Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. *Eur J Heart Fail.* 2008; **10**(11): 1102-7.
25. Nieman DC, Henson DA, Dumke CL, Oley K, McAnulty SR, Davis JM, et al. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Brain Behav Immun.* 2006; **20**(6): 578-84.
26. Tokmakidis SP, Kokkinidis EA, Smilios I, Douda H. The effects of ibuprofen on delayed muscle soreness and muscular performance after eccentric exercise. *J Strength Cond Res.* 2003; **17**(1): 53-9.
27. Hasson SM, Daniels JC, Divine JG, Niebuhr BR, Richmond S, Stein PG, et al. Effect of ibuprofen use on muscle soreness, damage, and performance: a preliminary investigation. *Med Sci Sports Exerc.* 1993; **25**(1): 9-17.
28. Donnelly AE, McCormick K, Maughan RJ, Whiting PH, Clarkson PM. Effects of a non-steroidal anti-inflammatory drug on delayed onset muscle soreness and indices of damage. *Br J Sports Med.* 1988; **22**(1): 35-8.
29. Lambert GP, Boylan M, Laventure JP, Bull A, Lanspa S. Effect of aspirin and ibuprofen on GI permeability during exercise. *Int J Sports Med.* 2007; **28**(9): 722-6.

- 1  
2  
3 30. Robertson JD, Maughan RJ, Davidson RJ. Faecal blood loss in response to  
4 exercise. *Br Med J (Clin Res Ed)*. 1987; **295**(6593): 303-5.  
5  
6 31. Simons SM, Kennedy RG. Gastrointestinal problems in runners. *Curr Sports*  
7 *Med Rep*. 2004; **3**(2): 112-6.  
8  
9 32. Page AJ, Reid SA, Speedy DB, Mulligan GP, Thompson J. Exercise-  
10 associated hyponatremia, renal function, and nonsteroidal antiinflammatory drug use  
11 in an ultraendurance mountain run. *Clin J Sport Med*. 2007; **17**(1): 43-8.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

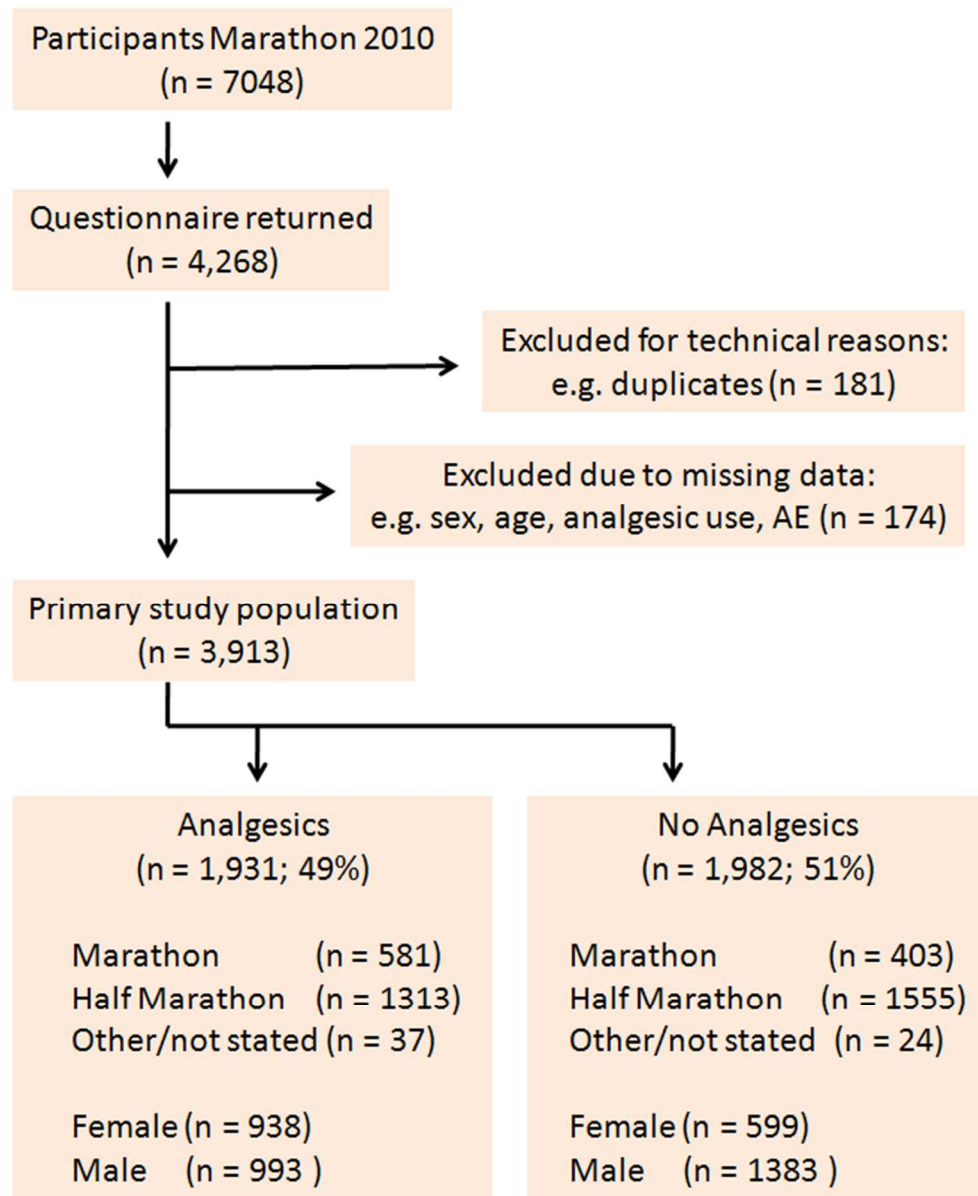


Figure 1: Flow chart of the evaluation of the marathon/half marathon running cohort. After the elimination of duplicates, almost 2,000 questionnaires were returned from each cohort. The distribution of marathon and half-marathon runners was similar in each treatment cohort. If participants entered races other than the marathon or half marathon (e.g. relays), or did not state which race they entered, they were captured in the 'other/not stated' cohort (AE; adverse event).  
56x68mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

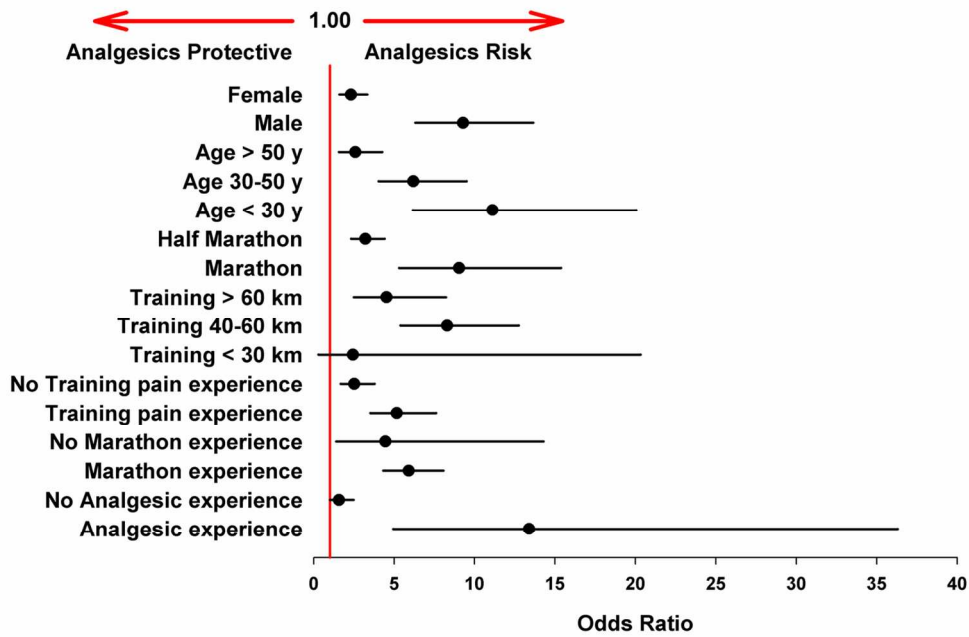


Figure 2: Risk of adverse events (AEs) within study subgroups (unadjusted). Odds ratios were estimated by binary linear regression analysis. Almost all subgroups show enhanced risk for AEs after analgesic use (odds ratios >1; error bars represent CI95%).  
124x79mm (300 x 300 DPI)

view only

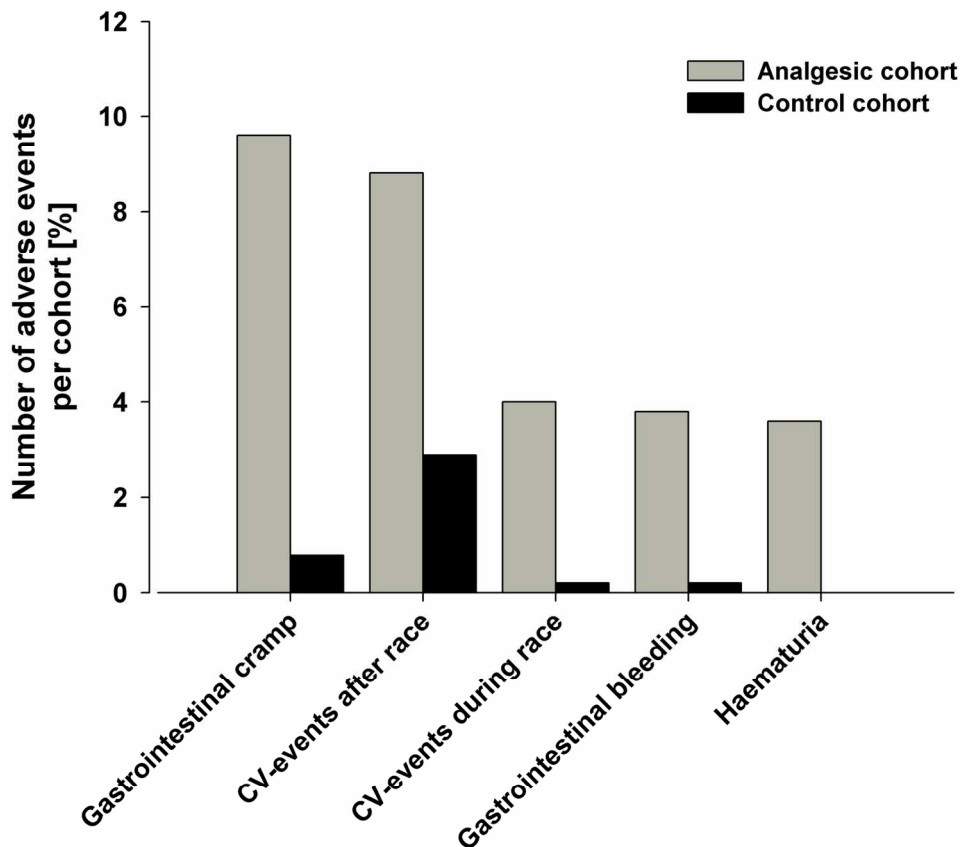


Figure 3: Incidence of adverse events (AEs, derived from Table S3)  
 Rounded percentages are given in Table S3  
 The differences between the groups were all highly significant;  $p < 0.001$ .  
 150x144mm (300 x 300 DPI)

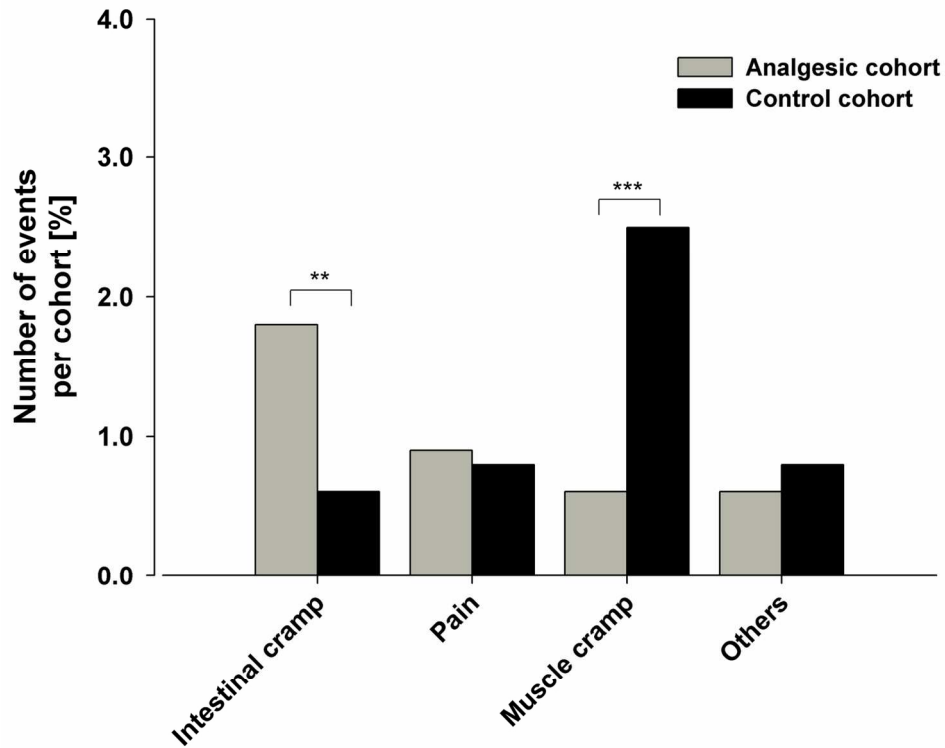


Figure 4: Reasons for premature termination of the race.  
Rounded percentages are given in Table S3

\*\*p<0.01

\*\*\*p<0.001

Note: the absolute numbers are small.  
137x117mm (300 x 300 DPI)

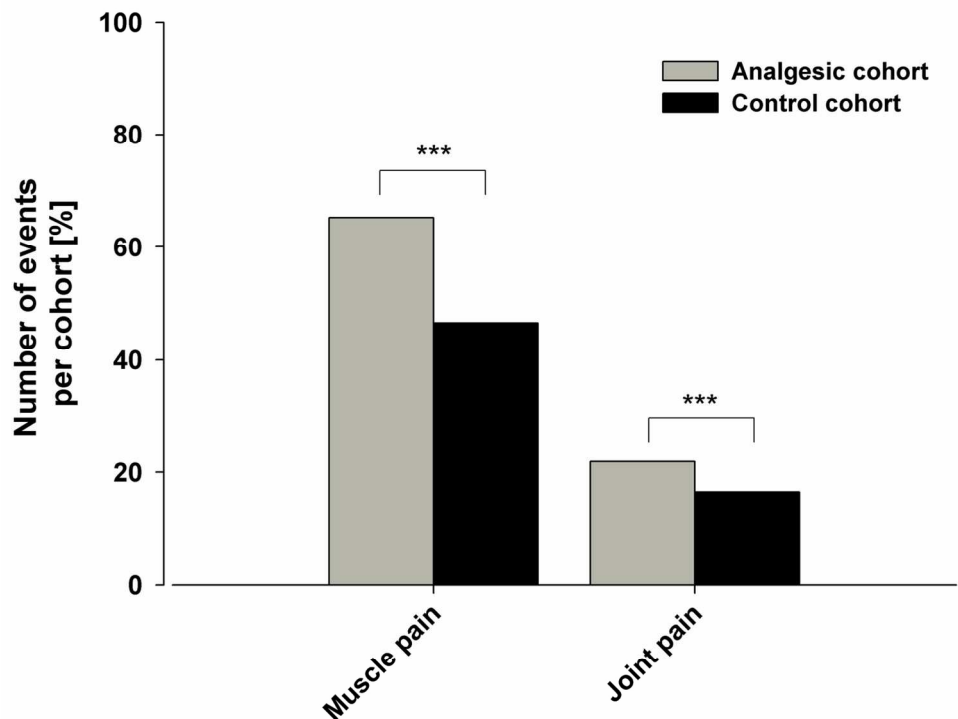


Figure 5: Percentage of runners experiencing muscle and/or joint pain after the race.  
 Rounded percentages are given in Table S3  
 The differences are highly significant (\*\*\*) p < 0.001.  
 131x108mm (300 x 300 DPI)

only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



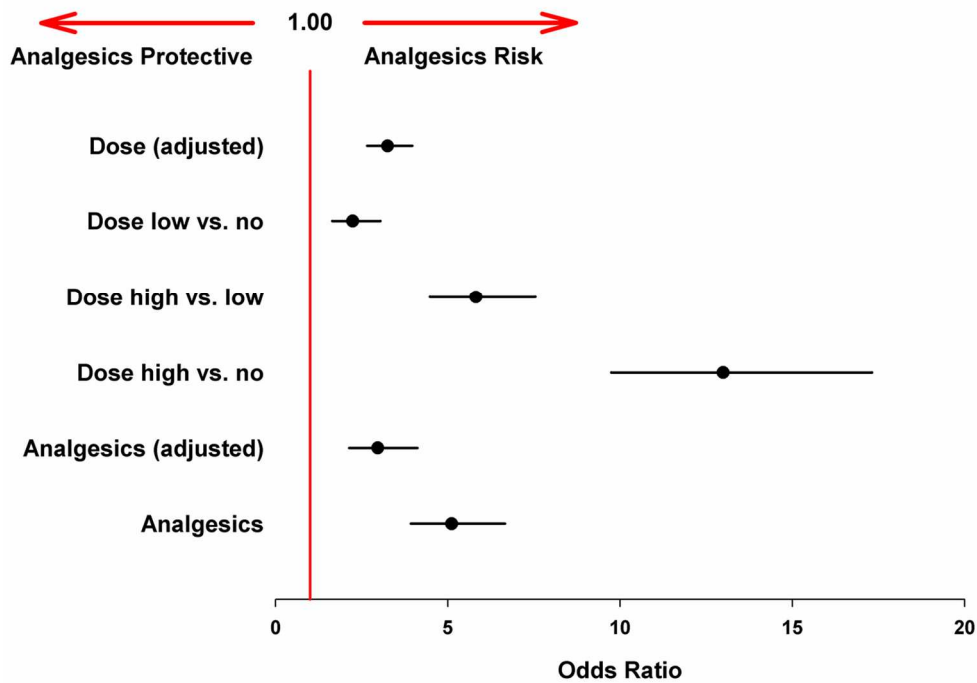


Figure 6: Adjusted adverse event (AE) risks for analgesic use and dose dependency  
There was a significant dose/AE relationship and reported odds ratios increased with increasing dose differences (Dose no = controls without analgesic use). Adjusted odds ratios were estimated by binary linear regression using possible confounders (error bars represent CI95%).  
124x85mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Bonn Marathon – Questionnaire for all sportsmen (2010)**

Participant number ..... (voluntary) to avoid double registration; anonymity assured!

1) Sex  female /  male

2)  non-professional or  professional athlete

3) Age (years) ..... J

4) Do have marathon experience?  yes /  no

5) Running performance/week within the last 3 months approximately .....km

6) Did you experience joint, muscle, or back pain during or after training?  yes /  no

7) Do you have experience with analgesics in connection with sport?  yes /  no

8) Did you ingest analgesics before today's marathon, such as diclofenac, aspirin, ibuprofen, naproxen, acetaminophen, dipyron?

11) Have you been informed about the risks of using analgesics in connection with a marathon?  yes /  no

12.) In which race did you participate:

a.  marathon,  half marathon,  relay (4 participants split the marathon distance)

b. Inline skating  full distance or  half distance

c. others: .....Km

13) During the race:

a. Hematuria  yes /  no

b. GI-cramps  yes /  no

c. GI-bleeds  yes /  no

d. CV-events (extrasystole, palpitation, tachycardia, and others)  yes /  no

14) After the race:

a. CV-events  yes /  no

b. Athralgia  yes /  no

c. Myalgia  yes /  no

15) I withdrew from the race for the following reason(s):

a.  I got tired of it

b.  I experienced severe pain

c.  I experienced GI-cramps

d.  I experienced muscle cramps

e.  other reasons: .....

1. Did you take analgesics before the start?  yes /  no

2. Did you have pain before the start of today's marathon?  yes /  no

3. Which analgesic and which dose did you take?

Ibuprofen Please select...	Diclofenac Please select...	Aspirin Please select...
Naproxen Please select...	Meloxicam Please select...	Celebrex Please select...
Etoricoxib Please select...	Acetaminophen Please select...	Dipyron Please select...

Others: .....

4.  prescription or  OTC?

9) Do you use analgesic during training?  yes /  no

10) Did a physician check your laboratory values while preparing for the marathon (e.g. kidney lab values)?  yes /  no

Many thanks for your cooperation.

Dr. med. Michael Küster, Bonn, April 2010

[Send / transfer data...](#)

Figure S1: Questionnaire supplied to marathon/half marathon participants. 103x68mm (300 x 300 DPI)

Review only

Table S1: Descriptive data on the participants

General information		Analgesics (49%)*			No Analgesics (51%)			Study population (100%)
		Female n=938 # of cases (%) <sup>#</sup>	Male n=993 # of cases (%)	All** Female and Male n=1931 (%)	Female n=599 # of cases (%)	Male n=1,383 # of cases (%)	All** Female and Male n=1,982 (%)	Total n=3,913 # of cases (%)
Age	≤30 y	67 (7)	57 (6)	124 (6)	345 (58)	443 (32)	788 (40)	912 (23)
	>30, ≤50 y	724 (77)	789 (80)	1513 (78)	141 (24)	707 (51)	848 (43)	2361 (60)
	>50 y	147 (16)	147 (15)	294 (15)	113 (19)	233 (17)	346 (18)	640 (16)
Experience	amateur	916 (98)	980 (99)	1896 (98)	588 (98)	1,355 (98)	1943 (98)	3839 (98)
	professional	4 (<1)	2 (<1)	6 (<1)	6 (1)	17 (1)	23 (1)	29 (1)
Previous marathon experience	yes	927 (99)	974 (98)	1901 (98)	398 (66)	1,121 (81)	1,519 (77)	3420 (87)
Training per week last 3 months	<40 km	4 (<1)	4 (<1)	8 (<1)	345 (58)	286 (21)	631 (32)	639 (16)
	40-60 km	729 (78)	508 (51)	1237 (64)	135 (23)	769 (56)	904 (46)	2141 (55)
	>60 km	201 (21)	478 (48)	679 (35)	119 (20)	328 (24)	447 (23)	1126 (29)
Pain during training	yes	573 (61)	382 (39)	955 (50)	193 (32)	308 (22)	501 (25)	1456 (37)
Analgesic use during sport	yes	534 (57)	906 (91)	1440 (75)	33 (6)	189 (14)	222 (11)	1662 (43)
Analgesic use during training	yes	129 (14)	254 (26)	383 (20)	7 (1)	9 (1)	16 (1)	399 (10)
Pain immediately before the race	yes	160 (17)	48 (5)	208 (11)	9 (2)	13 (1)	22 (1)	230 (6)
Lab check <sup>1</sup>	yes	64 (7)	52 (5)	116 (6)	62 (10)	120 (9)	182 (9)	298 (8)
Information received on the risk of analgesics	yes	34 (4)	30 (3)	64 (3)	58 (10)	76 (6)	134 (7)	198 (5)
	no	889 (95)	936 (95)	1825 (95)	520 (87)	1273 (92)	1793 (91)	3618 (93)
Race entered	Marathon	147 (16)	434	581 (30)	48 (8)	355 (26)	355 (26)	984 (25)

			(44)					
	Half marathon	778 (83)	535 (54)	1313 (68)	545 (91)	1,010 (73)	1,010 (73)	2868 (73)
	Other/not stated	13	24	37	6	18	18	61 (2)
Adverse events	yes	133 (14)	179 (18)	312 (16)	40 (7)	32 (2)	32 (2)	384 (10)

\*Percentages relate to the primary study population, and rounded to the nearest whole number.

# Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

\*\*The difference of all parameters was significant ( $p=0.002$  to  $p<0.001$ ) when analgesic and control cohort were compared (chi square tests, Fishers tests and U-tests).

<sup>1</sup> Lab check; Laboratory parameters tested before the race (e.g. kidney values; see question 10 in figure 1)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

Table S2: Use of analgesics before the marathon

Drugs	Doses	All n=1,931 # of cases (%) <sup>1</sup>	Female n=938 # of cases (%)	Male n=993 # of cases (%)
Diclofenac	≥ 100 mg (high)	219 (11)	91 (10)	128 (13)
	≤ 75 mg / unknown (low)	694 (36)	317 (34)	377 (38)
	None <sup>2</sup>	1,018	530	488
Ibuprofen	≥ 800 mg (high)	312 (16)	129 (14)	183 (18)
	≤ 600 mg / unknown (low)	410 (21)	217 (23)	193 (19)
	None	1,209	592	617
Aspirin	≥ 750 mg (high)	13 (<1)	8 (<1)	5 (<1)
	≤ 500 mg / unknown (low)	128 (7)	59 (6)	69 (7)
	None	1,790	871	919
Other analgesics <sup>3</sup>	High	68 (4)	44 (5)	24 (2)
	Low	107 (6)	70 (7)	37 (4)
	None	1,756	824	932
	Prescribed	42 (2)	21 (2)	21 (2)
	OTC	1,041 (54)	132 (14)	909 (92)
	Missing (data not reported)	848 (44)	785 (84)	63 (6)

<sup>1</sup> Percentages relate to the total number in the group, and rounded to the nearest whole number.

<sup>2</sup> The numbers in the 'no analgesic cohort', given for comparison.

<sup>3</sup> Other analgesics high dose / low dose, naproxen >500 mg / ≤ 500 mg or unknown, meloxicam ≥ 15 mg / ≤ 7.5 mg or unknown, celecoxib ≥ 400 mg / ≤ 200 mg or unknown, etoricoxib ≥ 120 mg / ≤ 90 mg or unknown, acetaminophen ≥ 1000 mg / ≤ 500 mg or unknown, dipyrrone ≥ 1000 mg / ≤ 500 mg or unknown.

Table S3: Adverse events during and after the marathon

Reports	Analgesics (49%)				No Analgesics (51%)			
	Half marathon n=1,313 # of cases (%) <sup>1</sup>	Marathon n=581 # of cases (%)	Other /not stated n=37 # of cases (%)	All n=1,931 # of cases (%)	Half marathon n=1,555 # of cases (%)	Marathon n=403 # of cases (%)	Other /not stated n=24 # of cases (%)	All n=1,982 # of cases (%)
<b>AEs<sup>2</sup></b>								
Urine blood	23 (2)	41 (7)	5 (14)	69 (4)	0 (0)	0 (0)	0 (0)	0 (0)
GI-cramp	84 (6)	98 (17)	3 (8)	185 (10)	7 (1)	8 (2)	0 (0)	15 (<1)
GI-bleeding	22 (2)	46 (8)	6 (16)	74 (4)	0 (0)	3 (1)	0 (0)	3 (<1)
CV-during race	11 (1)	66 (11)	1 (3)	78 (4)	3 (<1)	1 (<1)	0 (0)	4 (<1)
CV-post race	47 (4)	112 (19)	11 (30)	170 (9)	49 (3)	8 (2)	1 (4)	58 (3)
Total (individuals) <sup>3</sup>	138 (11)	158 (27)	16 (44)	312 (16)	55 (4)	16 (4)	1 (4)	72 (4)
<b>Reasons for premature race withdrawal</b>								
Intestinal cramp	35 (3)	0 (0)	0 (0)	35 (2)	12 (1)	0 (0)	0 (0)	12 (1)
Pain	14 (1)	3 (1)	0 (0)	17 (1)	16 (1)	0 (0)	0 (0)	16 (1)
Muscle cramp	9 (1)	1 (<1)	1 (3)	11 (1)	47 (3)	3 (1)	0 (0)	50 (3)
Others	8 (1)	3 (1)	1 (3)	12 (1)	14 (1)	1 (<1)	0 (0)	15 (1)
Total (individuals) <sup>4</sup>	66 (5)	7 (1)	2 (5)	75 (4)	89 (6)	4 (1)	0 (0)	93 (5)
<b>Pain post exercise</b>								
Joint	119 (9)	290 (50)	14 (38)	423 (22)	179 (12)	143 (36)	5 (21)	327 (17)
Muscle	929 (71)	308 (53)	22 (59)	1,259 (65)	642 (41)	271 (67)	10 (42)	923 (47)
Total (individuals)	955 (73)	323 (56)	23 (62)	1,301 (67)	710 (46)	274 (68)	11 (46)	995 (50)

<sup>1</sup> Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

<sup>2</sup> The difference of the incidence of all AEs was highly significant ( $p < 0.001$ ) when the "all" groups were combined, details and significance ranges are given in figure 4

<sup>3</sup> Number of individuals reporting AEs (a single individual may report >1 AE)

<sup>4</sup> The difference of withdrawals comparing the analgesic and control cohort was not significant ( $p = 0.237$ )

Table S4: Serious adverse events causing hospitalisation

No.	Drug (dose and time of intake)	Reason for intake	Patient (sex, age)	Symptoms (time after intake)	Diagnosis (means)	Therapy	Outcome
1	Ibuprofen (600 mg BS)	Fear of joint pain	Female, 38 years	Oliguria, dyspnoea	Haematuria, hyperkalaemia, proteinuria	Furosemide, fluid, electrolytes	Recovered
2	Ibuprofen (400 mg BS and 400 mg DR)	Unknown	Male, 47 years	Anuria, haematuria at day 2	Empty bladder	Furosemide	Recovered
3	Ibuprofen (600 mg BS)	Joint pain (former body-builder), impaired kidney function	Male, 57 years	Anuria, arrhythmia (RR 220/120 mmHg)	Anuria	Haemofiltration, electrolytes, furosemide for 10 days	Incompletely recovered
4	Aspirin (500 mg BS)	Dysmenorrhoea	Female, 28 years	Black stool at day 1	Bleeding gastric ulcer	Gastroscopic intervention, omeprazole	Recovered
5	Aspirin (500 mg BS)	Fear of joint pain	Male, 43 years	Vomiting (blood stained), GI-cramps at day 1, black stool	Toxic erosive gastritis	Omeprazole	Recovered
6	Aspirin (1000 mg BS)	Enhance performance	Male, 33 years	GI-cramps, vomiting (blood stained)	Haemorrhagic gastritis	Gastroscopy, pantozole	Recovered
7	Aspirin (1000 mg BS)	Joint pain	Male, 53 years	GI-cramps (evening), black stool	2 gastric ulcers	Gastroscopic intervention, omeprazole	Recovered
8	Aspirin (500 mg BS)	Foot pain	Male, 38 years (experienced in sports)	Chest pain during race	ECG: infarction (small)	No specific therapy	Recovered
9	Aspirin (100 mg; BS)	Fear of infarction	Male, 51 years (apparently healthy)	Chest pain	ECG, troponin test: (small) infarction	Intensive care, rehabilitation	Unknown

BS = before start of the race; DR = during race; ECG = electrocardiogram; RR = blood pressure



1 STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.



**Consumption of analgesics before a marathon increases the incidence of cardiovascular, gastrointestinal, and renal problems in a dose-dependent manner**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002090.R2
Article Type:	Research
Date Submitted by the Author:	30-Dec-2012
Complete List of Authors:	Kuester, Michael; Schmerzzentrum DGS, Renner, Bertold; FAU Erlangen-Nuremberg, Department of Experimental and Clinical Pharmacology and Toxicology Oppel, Pascal; FAU Erlangen-Nuremberg, Niederweis, Ursula; Universtitaetsklinikum Erlangen, Anaesthesiologische Klinik Brune, Kay; FAU Erlangen-Nuremberg, Department of Experimental and Clinical Pharmacology and Toxicology
<b>Primary Subject Heading</b>:	Sports and exercise medicine
Secondary Subject Heading:	Pharmacology and therapeutics, Cardiovascular medicine, Gastroenterology and hepatology, Renal medicine
Keywords:	PUBLIC HEALTH, SPORTS MEDICINE, Adverse events < THERAPEUTICS

SCHOLARONE™  
Manuscripts

Only

1  
2  
3 **Consumption of analgesics before a marathon increases the incidence of**  
4 **cardiovascular, gastrointestinal, and renal problems in a dose-dependent**  
5 **manner**  
6  
7

8  
9  
10  
11 M. Küster<sup>#</sup>, B. Renner<sup>#</sup>, P. Oppel, U. Niederweis, K. Brune\*  
12  
13

14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

\* Corresponding author

<sup>#</sup> Both authors contributed equally to the manuscript.

*Abstract word count = 268*

*Article word count = 3255*

*References count = 33*

## Article summary

### Article focus

- The participation in endurance sports, as marathon, is growing worldwide.
- Many amateurs engage in occasional endurance activities without adequate training, medical information, and experience.
- They try to overcome pain during and after sports by taking OTC-analgesics.

### Key message

- We hypothesized that the drugs taken before sports may increase the incidence of CV, GI and kidney damage without lowering pain during and after the exercise. An evaluation of about 4000 participants in a marathon resp. half-marathon supports this contention. Serious unwanted events occurred predominantly in users of analgesics. A benefit was not apparent.

### Strengths and limitations of this study

- This is the first investigation which relates unwanted drug effects during endurance sports to the use of analgesics. The effect was significant at OTC-doses and increased with higher doses. The incidence of organ damage was about eight times more frequent after analgesic use. Serious events requiring hospital admittance were reported only in the analgesic group. These findings pinpoint the unexpected risk of the prophylactic use of these drugs in sports.
- In our study, the role of confounders, as preexisting joint pain, could not be excluded.

**Abstract**

**Objectives:** To prevent pain inhibiting their performance, many athletes ingest over-the-counter (OTC) analgesics before competing. We aimed at defining the use of analgesics and the relation between OTC analgesic use/dose and adverse events (AEs) during and after the race, a relation that has not been investigated to date.

**Design:** Prospective (non-interventional) cohort study, using an on-line questionnaire

**Setting:** The Bonn marathon 2010

**Participants:** 3,913 out of 7,048 participants in the Bonn marathon 2010 returned their questionnaires.

**Primary and secondary outcomes:** Intensity of analgesic consumption before sports; Incidence of adverse events in the cohort of analgesic users as compared to non-users.

**Results:** There was no significant difference between premature race withdrawal rate in the analgesics cohort and the cohort who did not take analgesics ('controls'). However, race withdrawal because of gastrointestinal (GI) AEs was significantly more frequent in the analgesics cohort than in the control. Conversely, withdrawal because of muscle cramps was rare, but significantly more frequent in controls. The analgesics cohort had an almost ten times higher incidence of AEs (overall risk difference 13%). This incidence increased significantly with increasing analgesic dose. Nine respondents reported temporary hospital admittance: three for temporary kidney failure (post ibuprofen ingestion), four with bleeds (post aspirin ingestion), and two cardiac infarctions (post aspirin ingestion). None of the control reported hospital admittance.

**Conclusions:** The use of analgesics before participating in endurance sports may cause many, potentially serious, unwanted AEs that increase with increasing analgesic dose. Analgesic use before endurance sports appears to pose an unrecognized medical problem as yet. If verifiable in other endurance sports, it requires the attention of physicians and regulatory authorities.

## **Introduction**

Endurance sports are becoming increasingly popular. However, recent research has shown that physical activity does not automatically result in better health, but could exacerbate cardiovascular (CV) disease[1 2]. This may be related to the inhibition of cyclooxygenases by non-steroidal anti-inflammatory drugs (NSAIDs), including 'over the counter' (OTC) analgesics, that are known to exacerbate atherosclerosis[3] and CV problems in some patients[4].

Previous studies have shown that the use and abuse of analgesics in sports is frequent and possibly dangerous[5-11], and that the incidence and severity of electrolyte disturbances[12 13], gastrointestinal (GI)[14], and renal adverse events (AEs)[15-17] during and after racing double after taking analgesics. However, these studies investigated AEs in isolation and did not investigate a dose response relationship.

In a preliminary study, we interviewed 1,024 participants of the Bonn marathon/half marathon, and collected information on their training, fitness, and drug use<sup>[5]</sup>. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice<sup>[5]</sup>. These results were confirmed by Gorski et al[18].

We now report a follow-up study aiming at defining the use of analgesics in relation to premature race withdrawal, and AEs occurring during and after racing. In this report, we summarize NSAIDs and other cyclooxygenase-inhibitors including acetaminophen (paracetamol) as analgesics.

## **Methods**

### **Study population**

The investigation relied on a questionnaire made available to all participants of the Bonn marathon/half marathon 2010 on paper and via the internet by the organizer together with information on the purpose of the investigation. Participating in the study was recommended by the organizer (Figure S1). The questionnaire examined:

1. Background epidemiology: age, sex, running experience, use of analgesics during training/in previous races, and details of previous training.
2. Medication use before the race: name and dose of drugs taken before the race start, and any medical advice received.
3. During and after racing: completion/reasons for premature withdrawal from the race, and AEs.

### Study design

The study was conducted according to the Declaration of Helsinki on biomedical research involving human subjects (Somerset West amendment). Advertisement and study information was provided by the local organizer. All questionnaires returned were in an anonymised form which made identification of single participants impossible. The integrity of the participants remained unimpaired. After having consulted the local ethics committee, it was agreed that a formal application to the Institutional Ethics Review Board (IRB) was not required according to professional regulations. The scientific quality of the study design was not subjected to the control of the IRB.

The case reports (serious cases) were regarded as request for medical advice and handled as such by MK (MD) who preserved the anonymity of these “patients”.

All data sheets (received questionnaires) were checked for completeness and duplicates using SPSS software version 19, followed by inspection by two researchers.

### Outcome measures

The primary hypothesis was that consumption of analgesics is associated with an increased incidence of AEs. An AE was included in the analysis if one or more of the following events were recorded on the questionnaire: GI cramps and bleeds, haematuria, or CV events (e.g. arrhythmia, palpitation).

### Statistical analysis

AEs and reasons for premature race withdrawal were tabulated according to a number of population-based factors which may influence drug use or AE incidence. Cross-tables, the chi square test, or Fisher’s test were used to analyse subgroups to



1  
2  
3 establish relative risk differences and possible confounding factors. Drug doses (no  
4 drug, low dose, and high dose) were used to determine possible dose-related effects  
5 on AE incidence and race withdrawal.  
6  
7

8  
9 A binary regression model was used to estimate odds ratios and 95% confidence  
10 intervals for AE incidence in subgroups and in the primary study population, with  
11 adjustment for confounding factors. Analyses were conducted using SPSS software  
12 version 19. Statistical tests were two-sided, and p-values less than 0.05 were  
13 considered statistically significant. AEs from respondents who did not state which  
14 race they entered were not included in the marathon/half marathon sub-group  
15 analysis.  
16  
17  
18  
19

## 20 21 **Results**

22  
23 4,268 completed questionnaires were returned. More than 90% of the questionnaires  
24 were received by day 10, the rest within day seventeen after the race. Approximately  
25 4% were identified as duplicates, and were excluded from the analysis (Figure 1). An  
26 additional 4% of questionnaires were excluded because primary data were missing  
27 (i.e. age, sex, drug use, AEs).  
28  
29  
30  
31

32  
33 The remaining 3,913 completed questionnaires constituted the primary study  
34 population, representing 56% of the participants in the Bonn marathon/half marathon  
35 2010 (Figure 1). Nearly half of the study cohort used analgesic before the actual race  
36 ('analgesic cohort': n=1931, 49%) and 51% reported not to have used any analgesic  
37 ('control group': n=1982; Figure 1).  
38  
39  
40

## 41 Background epidemiology

42  
43  
44 Descriptive epidemiological data are given in Table S1 (supplementary information).  
45 Overall, there were more men than women (2,376 vs. 1,537), and men were slightly  
46 older on average (means  $\pm$ SD: 40  $\pm$ 10 vs. 39  $\pm$ 11 years). Males and females were  
47 younger in the control group (means  $\pm$ SD analgesic group: male 43  $\pm$ 8, female 42  $\pm$ 8  
48 years vs. control group: male 38  $\pm$ 12, female 34  $\pm$ 13 years). Most respondents had  
49 previous marathon experience (overall 87%). In the analgesics cohort, 20% had also  
50 taken analgesics during training (male 26% vs. female 14%), compared with 1% of  
51 the control group. Of the analgesics cohort, 11% recorded pain before the race  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 (compared with 1% of controls), and 16% recorded AEs during/after racing  
4 (compared with 2% of controls).  
5  
6

### 7 Medication use before racing

8  
9 In total, 1,931 respondents ingested analgesics before racing, to retard or avoid pain  
10 during the races and thereafter. They used analgesics immediately before the race.  
11 Most of the analgesics (54%) were taken without prescription (Table S2), and  
12 significantly more women (61%) took analgesics than men (42%).  
13  
14  
15  
16

17 The most frequently used analgesic was diclofenac, used by 47% of the analgesics  
18 cohort before the race (Table S2). Many athletes (11%) resorted to supra-OTC doses  
19 of diclofenac (over 100 mg). The second most commonly used analgesic was  
20 ibuprofen, and 43 % of those who took ibuprofen ingested  $\geq 800$  mg (twice as the  
21 recommended OTC single dose). Aspirin was used less frequently, and mostly at low  
22 therapeutic doses. Acetaminophen, celecoxib, dipyron, etoricoxib, meloxicam, and  
23 naproxen were also used, although these drugs were taken by comparatively few  
24 athletes and are grouped as 'other analgesics' in the analysis (Table S2).  
25  
26  
27  
28  
29  
30

31 Of all respondents, 93% declared that they were not informed about the risks of using  
32 analgesics in connection with sports endurance (Table S1).  
33  
34

### 35 Events during and after the race:

36  
37 The incidence of reported AEs was significantly higher in runners of the full marathon  
38 compared with the half-marathon (18% vs 7%;  $p < 0.001$ ). Additionally, the analgesic  
39 related AE risk in the full marathon cohort was significantly higher than in the half  
40 marathon cohort (odds 9.04; 95% CI 5.31-15.39 vs 3.20; CI 2.32-4.42. Figure 2).  
41  
42  
43  
44

45 There were similar numbers of half marathon and marathon runners in the analgesics  
46 cohort compared with controls.  
47  
48

49 A four to ten times higher incidence of each type of AE was observed in the  
50 analgesics cohort compared with controls (overall incidence 16% vs 4%. Table S3,  
51 Figure 3), with a calculated risk difference of 13%. The difference in the incidence of  
52 AEs between the two cohorts was most prominent with respect to GI cramps and CV-  
53 events (after race). In the analgesics cohort, GI cramps were the most frequent AE  
54 (reported by 14% of the cohort), followed by CV AEs after the race (9%). In the  
55  
56  
57  
58  
59  
60

1  
2  
3 controls, CV AEs after the race were the most frequently reported AE (3%, Table S3).  
4 Notably, haematuria was reported only in the analgesics cohort. The differences in  
5 the incidence of all AEs were highly significant between the two groups ( $p < 0.001$ ,  
6 Table S3, Figure 3).  
7  
8

9  
10 No significant difference was found between the analgesics cohort and controls in  
11 terms of premature race withdrawal overall (Table S3,  $p = 0.237$ ). Race withdrawal  
12 because of muscle cramps occurred significantly more often in controls (3% vs 1%,  
13 Table S3, Figure 4,  $p < 0.001$ ), but the absolute difference was small. Conversely,  
14 intestinal cramps were significantly more frequently blamed for race withdrawal in the  
15 analgesics cohort compared with controls (2% vs 1%;  $p < 0.01$ , Table S3, Figure 4).  
16  
17

18 Joint and muscle pain after the race were significantly more frequent in the  
19 analgesics cohort than in controls (1,301 vs 955 respondents,  $p < 0.001$ , Table S3,  
20 Figure 5).  
21

22 The overall risk for analgesic related AEs was estimated at 5.1 (95% CI 3.9-6.7;  
23  $p < 0.001$ , Figure 6), giving a 'number needed to harm' of eight treated participants. In  
24 a subsequent subgroup analysis for sex, age, training, marathon/half marathon run,  
25 and analgesic experience, an enhanced risks (odds ratio) for the different subgroups  
26 was detected, but this was very variable (1.6-13.4, Figure 2). Therefore, these  
27 subgroup parameters were included in a regression analysis which resulted in a  
28 comparable adjusted analgesic related risk of 3.0 (95% CI 2.1-4.1;  $p < 0.001$ , Figure  
29 6).  
30  
31

32 To investigate if the incidence of AEs was dose-dependent, a risk estimation of the  
33 size of the dose was conducted. The high dose resulted in a significantly higher risk  
34 of AEs compared with the lower dose or controls. Even the low dose group presented  
35 a higher risk of AEs compared with controls (Figure 6). This further adjusted  
36 regression model showed a statistically significant increased risk at rising doses,  
37 meaning that increasing the dose can increase the risk of AEs by three times (odds  
38 ratio 3.2; 95% CI, 2.7-4.0,  $p < 0.001$ , Figure 6).  
39  
40

41 Finally, the association of analgesic use with distinct side effect profiles was  
42 analysed. The ingestion of all three drugs used most frequently (aspirin, diclofenac,  
43 and ibuprofen) was associated with AEs in a dose-dependent manner (Table 1).  
44 Overall, the "drug related" incidence (defined as the percentage of respondents  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 reporting AEs out of the total number of respondents taking a particular analgesic)  
4 was highest with aspirin, followed by ibuprofen, and lowest with diclofenac in both  
5 subgroups (high and low dose of analgesics; Table 1). At high doses, 10% of  
6 diclofenac users, 52% of ibuprofen users, and 87% of aspirin users experienced AEs  
7 (Table 1). Aspirin was associated with relatively numerous GI or kidney bleeds,  
8 compared with the other analgesics (reported by 49% of the “high dose” Aspirin  
9 users).

### 10 11 12 **Serious cases**

13  
14  
15 In addition to the evaluation by questionnaire, the participants of the Bonn  
16 marathon/half marathon 2010 were encouraged to report serious events which  
17 required hospital admittance during the 3 days following the race to the physician in  
18 charge, this evaluation (MK). Nine case reports of hospital admittance were received  
19 (Table S4 by MK), all of which concerned participants of the analgesics cohort. Three  
20 athletes (numbers 1-3, Table S4) reported anuria/oliguria which started the day after  
21 the race and lasted for up to three days. In two cases this AE resolved after a  
22 hyperuric period, and one respondent reported ongoing renal problems (haematuria  
23 for 2 days - number 3, Table 5). In all three cases, moderate doses of ibuprofen (2 x  
24 400 mg, 600 mg, and 600 mg) were taken before and during the race together with  
25 large amounts of fluid.

26  
27  
28 Four respondents (numbers 4-7, Table S4) reported hospital admittance because of  
29 GI-bleeding (black stools and vomiting blood). Gastroendoscopic evaluation revealed  
30 at least one intervention requiring bleeding ulcer. The patients were further monitored  
31 endoscopically and given proton pump inhibitors. All four respondents had ingested  
32 moderate amounts of aspirin (500-1,000 mg) before the race, and all were released  
33 after a few days without obvious sequelae.

34  
35  
36 Two more respondents (numbers 8 and 9, Table S4) were hospitalised after ingesting  
37 aspirin before the race. One took a 100 mg dose to prevent infarction, the other took  
38 500 mg because of mild foot pain. Both respondents complained of chest pain,  
39 angina, and arrhythmia the day after racing, and both suffered cardiac infarctions.  
40 Both athletes recovered, although some cardiac damage remained in one  
41 respondent.

1  
2  
3 These nine cases are well documented (Table S4). However, it should be noted that  
4 since reporting was spontaneous and voluntary, and a lack of corresponding hospital  
5 admittance in the control cohort could not be proven. Also we do not know if the  
6 patients/participants filled and submitted an (anonymized) questionnaire.  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Discussion

It is known that many professional and amateur athletes use analgesics prophylactically to increase performance and prevent pain[6-17 19 20].

A recent publication in the NEJM[12] warned that over-hydration during marathons might increase the risk of CV events. However, this study did not investigate the association between the use of drugs and CV problems. Recently, we reported that two-thirds of the participants of a marathon took analgesics before the start[21]. This investigation showed that most athletes taking analgesics had taken supra-therapeutic doses. Similar data were reported by Gorski et al[18]. However, these studies did not investigate the use of analgesics and premature race withdrawal, nor did they systematically record performance and incidence of AEs.

The current study was designed to test the hypothesis that cyclooxygenase inhibitors contribute to the development of AEs, which is possible since these drugs block the protective effects of prostaglandins on GI, CV, and renal function. We hypothesize that their use is likely to suspend the mucosa- and kidney-protective[3] effects of PGE<sub>2</sub>/PGI<sub>2</sub>, thus augmenting the damaging effect of diminished blood flow[22] and oxygen supply for the GI mucosa and kidney[23]. Moreover, it was postulated that marathon runs could decrease the barrier function of the intestinal mucosa, further increasing the absorption of bacterial toxins from the gut[24], and that repeated inhibition of the production of endothelium-produced PGI<sub>2</sub> during CV stress, e.g. intensive exercise, may accelerate atherosclerosis[1 2 25].

This study analysed respondents for age, sex, training status, drug use (including doses), race completion, and AEs that occurred during the race and afterwards. To the best of our knowledge, this study shows for the first time that the administration of analgesics before a marathon/half-marathon can significantly increase AEs, and these increase with increasing analgesic dose. This increased incidence of AEs is dramatic; e.g. 4% of respondents in the analgesics cohort reported haematuria compared with 0% of controls. Moreover, nine respondents reported hospital admittance caused by either temporary kidney failure, bleeding ulcers, or cardiac infarctions. All these serious events occurred in the analgesics cohort.

Altogether, these data do not support the contention that taking analgesics before racing improves the ability to complete the race or to prevent AEs thereafter.

Four aspects of this study deserve an in-depth discussion.

1. *Analgesics taken prophylactically before racing do not prevent pain*

Analysis of the pain reported by respondents before and after racing showed no major identifiable advantages gained from taking analgesics. Muscle cramps were reported as a reason for premature race withdrawal marginally less frequently in the analgesics cohort compared with the control. Although the difference was significant ( $p < 0.001$ ), the small sample size does not allow concrete conclusions to be drawn, particularly in the context of the parameters of overall pain during racing and intestinal cramps. There were significantly more intestinal cramps in the analgesics cohort ( $p < 0.001$ ) compared with the control, and more muscle and joint pain were reported in the analgesics cohort after racing than in the control.

This result supports observations reported by Nieman *et al.*, who found that the intake of ibuprofen at regular intervals during an ultra-marathon race did not decrease muscle soreness in the days afterwards[26]. This may be explained by the fact that all the drugs investigated (diclofenac, ibuprofen, and aspirin) display a short elimination half-life of around two hours, which would make effects several hours after the ingestion of the drugs rather unlikely. In the report by Nieman *et al.*, the last dose of ibuprofen was taken several hours before finishing the race, and so the lack of influence on post-race pain is not surprising. Several research groups have reported the analgesic effects of NSAIDs in volunteers undertaking physical exercise. However, in these studies, the drugs were given after exercise, not before, which makes their reported analgesic effect plausible and recognisable[27-29].

In conclusion, our data indicate that the intake of cyclooxygenase inhibitor analgesics does not offer protection from pain during or after a marathon/half marathon compared with controls. However definitive proof of this contention would warrant a prospective, randomised cohort study.

2. *Analgesics contribute to AEs*

This study investigated if cyclooxygenase inhibitors contribute to the AEs observed frequently in endurance sports[24 30]. All of the AEs observed



1  
2  
3 frequently during marathons, i.e. CV events, GI cramps/bleeds, and renal  
4 dysfunction, occurred much more frequently in the analgesics cohort  
5 compared with the control. This effect was not dependent on the type of  
6 analgesic, i.e. all three drugs used frequently caused an increase in CV, GI,  
7 and renal AEs. This supports our hypothesis that the use of cyclooxygenase  
8 inhibitors before the start of a race may be damaging because tissue  
9 protection that is usually provided by prostaglandins may be impaired,  
10 triggering GI, CV, and renal AEs. These effects again suggest that the use of  
11 cyclooxygenase inhibitors before and during a marathon/half marathon race  
12 may be dangerous and should be avoided.  
13  
14  
15  
16  
17  
18  
19

### 20 3. *The AE profile of different analgesics is different*

21  
22 Although the use of analgesics increases the overall incidence of AEs, all nine  
23 serious events reported to us which led to temporary hospital admittance  
24 concur with the pattern of AEs seen per drug in the rest of the respondents.  
25 The three temporary kidney failure cases (all of whom had ingested ibuprofen)  
26 correspond with the relatively high incidence of renal AEs in the ibuprofen  
27 group (Table 1). Moreover, the bleeding ulcers observed in the aspirin group  
28 mirror the high incidence of GI problems seen after the intake of aspirin.  
29 Somewhat surprising is the fact that both cardiac infarctions occurred in the  
30 aspirin group. This is interesting since aspirin should have protected from such  
31 events. However, definite conclusions cannot be drawn because of the small  
32 sample size. Overall, our observations are in line with previous reports[1 31-  
33 33].  
34  
35  
36  
37  
38  
39  
40  
41  
42

### 43 4. *Limitations of the study*

44  
45 A double-blind, randomized, cross-over design for any trial is the gold  
46 standard. However, this is obviously impractical in these circumstances.  
47 Despite the relatively high return of questionnaires, there was still no  
48 information available for half of the marathon/half marathon participants, and  
49 many confounding factors such as BMI, use of other drugs etc. were not  
50 investigated. Implementing a higher number of items in our questionnaire in  
51 order to cover additional confounders will have limited participant's compliance  
52 and the overall response rate. Although the two cohorts were of similar sizes,  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 there are differences between them with respect to age, sex, training, and  
4 drug experience (a contribution of long term use of OTC analgesic on the  
5 incidence of AEs cannot be excluded), which may also have influenced the  
6 outcome. However, the considerable homogeneity of the AEs seen throughout  
7 all subgroups supports the overall contention that cyclooxygenase inhibitors  
8 taken before and during a marathon/half marathon race increase the risks of  
9 AEs substantially, without measurable benefit in terms of race completion.  
10  
11  
12  
13  
14

15 Taken together, our data indicate that the widespread use of cyclooxygenase  
16 inhibitors in connection with endurance sports is potentially damaging. In our study,  
17 the administration of analgesics before the start of a race did not prevent post-  
18 exercise pain or significantly reduce the premature withdrawal rate compared with the  
19 control. Conversely, the use of cyclooxygenase inhibitors considerably increased the  
20 incidence of GI, renal, and CV AEs. We conclude that the use of analgesics before  
21 and during endurance sports may pose a serious health problem that should be  
22 addressed. Our investigation has also shown a worrying lack of education about  
23 these AEs within the participants of the Bonn 2010 marathon/half marathon, which  
24 may highlight a larger problem if mirrored in the endurance sport community in  
25 general. We would encourage greater awareness of the possible AEs of these drugs,  
26 particularly among endurance sports enthusiasts.  
27  
28  
29  
30  
31  
32  
33  
34  
35

36 Further investigations are warranted to examine if the use of analgesics before and  
37 during sports activities should be avoided altogether.  
38  
39  
40  
41  
42

### 43 **Acknowledgements**

44  
45 K. Brune is Doerenkamp-Professor. He was supported by the Hertie Foundation.  
46 The authors declare no conflict of interest.  
47 The authors acknowledge the assistance of a medical writer in the editing and  
48 language checking of this manuscript.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1: Incidence of adverse events (AEs) in relation to the analgesic used

Adverse events	Diclofenac n=913		Ibuprofen n=722		Aspirin n=141		Other analgesics n=175	
	Low dose n=693 no. of reports (%) <sup>1</sup>	High dose n=220 no. of reports (%)	Low dose n=410 no. of reports (%)	High dose n=312 no. of reports (%)	Low dose n=102 no. of reports (%)	High dose n=39 no. of reports (%)	Low dose n=107 no. of reports (%)	High dose n=68 no. of reports (%)
Urine blood	6 (1)	5 (2)	5 (1)	45 (14)	7 (7)	19 (49)	1 (1)	1 (2)
GI-cramp	16 (2)	5 (2)	52 (13)	89 (29)	11 (11)	9 (23)	4 (4)	9 (13)
GI-bleeding	2 (<1)	8 (4)	13 (3)	39 (13)	9 (9)	19 (49)	1 (1)	2 (3)
CV – during race	2 (<1)	0 (0)	40 (10)	28 (9)	3 (3)	8 (21)	5 (5)	0 (0)
CV – post race	4 (1)	8 (4)	44 (11)	97 (31)	11 (11)	12 (31)	3 (3)	3 (4)
Total (individuals) <sup>2</sup>	25	22	56	163	25	34	11	12
Drug related AE incidence	4%	10%	14%	52%	25%	34%	11%	12%

<sup>1</sup> Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

<sup>2</sup> Number of individuals reporting AEs (a single individual may report >1 AE)

See Table S2 for definition of dose sizes

### Competing Interests

All authors have no conflict of interest. The results of this investigation do not support the use of certain drugs, but rather point out that all so called cyclooxygenase inhibitors, taken before endurance sports, may carry serious risks. Patient consent appears not required as all patients remain anonymous. Funding was not drug industry related. We declare that a similar paper is not in preparation, submitted, or under publication.

### Funding

Hertie Foundation - supported KB by giving a grant for office requisites

### Data Sharing

No additional data available.

**References:**

1. Schwartz JG, Merkel-Kraus, S., Duval, S., et al. Does longterm endurance running enhance or inhibit coronary artery plaque formation? A prospective multidetector CTA study of men completing marathons for least 25 consecutive years. *J Am Coll Cardiol* 2010;**55**(10A):A.173.E1624
2. Mohlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J* 2008;**29**(15):1903-10 doi: 10.1093/eurheartj/ehn163[published Online First: Epub Date]].
3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol* 2011;**31**(5):986-1000 doi: 10.1161/ATVBAHA.110.207449[published Online First: Epub Date]].
4. Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;**368**(9549):1771-81 doi: 10.1016/S0140-6736(06)69666-9[published Online First: Epub Date]].
5. Brune K, Niederweis U, Krämer B. Sport und Schmerzmittel: Unheilige Allianz zum Schaden der Niere. *Deutsches Ärzteblatt* 2008;**105**(37):1894-900
6. Tscholl P, Alonso JM, Dolle G, et al. The use of drugs and nutritional supplements in top-level track and field athletes. *Am J Sports Med* 2010;**38**(1):133-40 doi: 10.1177/0363546509344071[published Online First: Epub Date]].
7. Tscholl P, Feddermann N, Junge A, et al. The use and abuse of painkillers in international soccer: data from 6 FIFA tournaments for female and youth players. *Am J Sports Med* 2009;**37**(2):260-5 doi: 10.1177/0363546508324307[published Online First: Epub Date]].
8. 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[published Online First: Epub Date]].
9. Taioli E. Use of permitted drugs in Italian professional soccer players. *Br J Sports Med* 2007;**41**(7):439-41 doi: 10.1136/bjism.2006.034405[published Online First: Epub Date]].
10. Alaranta A, Alaranta H, Heliövaara M, et al. Ample use of physician-prescribed medications in Finnish elite athletes. *Int J Sports Med* 2006;**27**(11):919-25 doi: 10.1055/s-2006-923811[published Online First: Epub Date]].
11. Da Silva ER, De Rose EH, Ribeiro JP, et al. Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007). *Br J Sports Med* 2011;**45**(2):91-4 doi: 10.1136/bjism.2009.065342[published Online First: Epub Date]].
12. Almond CS, Shin AY, Fortescue EB, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med* 2005;**352**(15):1550-6 doi: 10.1056/NEJMoa043901[published Online First: Epub Date]].
13. Wharam PC, Speedy DB, Noakes TD, et al. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc* 2006;**38**(4):618-22 doi: 10.1249/01.mss.0000210209.40694.09[published Online First: Epub Date]].
14. Halvorsen FA, Lyng J, Ritland S. Gastrointestinal bleeding in marathon runners. *Scand J Gastroenterol* 1986;**21**(4):493-7
15. Le Meur Y, Paraf F, Szelag JC, et al. Acute renal failure in a marathon runner: role of glomerular bleeding in tubular injury. *Am J Med* 1998;**105**(3):251-2
16. Irving RA, Noakes TD, Raine RI, et al. Transient oliguria with renal tubular dysfunction after a 90 km running race. *Med Sci Sports Exerc* 1990;**22**(6):756-61

17. Boulter J, Noakes TD, Hew-Butler T. Acute renal failure in four Comrades Marathon runners ingesting the same electrolyte supplement: coincidence or causation? *S Afr Med J* 2011;**101**(12):876-8
18. Gorski T, Cadore EL, Pinto SS, et al. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med* 2011;**45**(2):85-90 doi: 10.1136/bjism.2009.062166[published Online First: Epub Date]].
19. Doraiswamy PM, Hoffman B.M. Fitness and the Brain: Can a Walk a Day Keep Alzheimer's Away? *Scientific American* 2008;**4**
20. Lippi G, Franchini M, Guidi GC, et al. Non-steroidal anti-inflammatory drugs in athletes. *Br J Sports Med* 2006;**40**(8):661-2; discussion 62-3 doi: 10.1136/bjism.2006.027342[published Online First: Epub Date]].
21. Brune K, Niederweis U, Kaufmann A, et al. [Drug use in participants of the Bonn Marthon 2009]. *MMW Fortschr Med* 2009;**151**(40):39-41
22. Kehl O, Jager K, Munch R, et al. [Mesenterial anemia as a cause of jogging anemia?]. *Schweiz Med Wochenschr* 1986;**116**(29):974-6
23. Noakes TD, Sharwood K, Speedy D, et al. Three independent biological mechanisms cause exercise-associated hyponatremia: evidence from 2,135 weighed competitive athletic performances. *Proc Natl Acad Sci U S A* 2005;**102**(51):18550-5 doi: 10.1073/pnas.0509096102[published Online First: Epub Date]].
24. Pals KL, Chang RT, Ryan AJ, et al. Effect of running intensity on intestinal permeability. *J Appl Physiol* 1997;**82**(2):571-6
25. Scott PA, Kingsley GH, Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. *Eur J Heart Fail* 2008;**10**(11):1102-7 doi: 10.1016/j.ejheart.2008.07.013[published Online First: Epub Date]].
26. Nieman DC, Henson DA, Dumke CL, et al. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Brain Behav Immun* 2006;**20**(6):578-84 doi: 10.1016/j.bbi.2006.02.001[published Online First: Epub Date]].
27. Tokmakidis SP, Kokkinidis EA, Smilios I, et al. The effects of ibuprofen on delayed muscle soreness and muscular performance after eccentric exercise. *J Strength Cond Res* 2003;**17**(1):53-9
28. Hasson SM, Daniels JC, Divine JG, et al. Effect of ibuprofen use on muscle soreness, damage, and performance: a preliminary investigation. *Med Sci Sports Exerc* 1993;**25**(1):9-17
29. Donnelly AE, McCormick K, Maughan RJ, et al. Effects of a non-steroidal anti-inflammatory drug on delayed onset muscle soreness and indices of damage. *Br J Sports Med* 1988;**22**(1):35-8
30. Lambert GP, Boylan M, Laventure JP, et al. Effect of aspirin and ibuprofen on GI permeability during exercise. *Int J Sports Med* 2007;**28**(9):722-6 doi: 10.1055/s-2007-964891[published Online First: Epub Date]].
31. Robertson JD, Maughan RJ, Davidson RJ. Faecal blood loss in response to exercise. *Br Med J (Clin Res Ed)* 1987;**295**(6593):303-5
32. Simons SM, Kennedy RG. Gastrointestinal problems in runners. *Curr Sports Med Rep* 2004;**3**(2):112-6
33. Page AJ, Reid SA, Speedy DB, et al. Exercise-associated hyponatremia, renal function, and nonsteroidal antiinflammatory drug use in an ultraendurance mountain run. *Clin J Sport Med* 2007;**17**(1):43-8 doi: 10.1097/JSM.0b013e31802b5be9[published Online First: Epub Date]].

1  
2  
3 **Consumption of analgesics before a marathon increases the incidence of**  
4 **cardiovascular, gastrointestinal, and renal problems in a dose-dependent**  
5 **manner**  
6  
7  
8  
9

10  
11 M. Küster<sup>#</sup>, B. Renner<sup>#</sup>, P. Oppel, U. Niederweis, K. Brune\*  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

43 \* Corresponding author  
44

45 <sup>#</sup> Both authors contributed equally to the manuscript.  
46  
47  
48

49 *Abstract word count = 291268*

50 *Article word count = 32553210*

51  
52 *References count = 3233*  
53  
54  
55  
56  
57  
58  
59  
60

## Article summary

### Article focus

- The participation in endurance sports, as marathon, is growing worldwide.
- Many amateurs engage in occasional endurance activities without adequate training, medical information, and experience.
- They try to overcome pain during and after sports by taking OTC-analgesics.

### Key message

- We hypothesized that the drugs taken before sports may increase the incidence of CV, GI and kidney damage without lowering pain during and after the exercise. An evaluation of about 4000 participants in a marathon resp. half-marathon supports this contention. Serious unwanted events occurred predominantly in users of analgesics. A benefit was not apparent.

### Strengths and limitations of this study

- This is the first investigation which relates unwanted drug effects during endurance sports to the use of analgesics. The effect was significant at OTC-doses and increased with higher doses. The incidence of organ damage was about eight times more frequent after analgesic use. Serious events requiring hospital admittance ~~hospitalisation~~ were reported only in the analgesic group. These findings pinpoint the unexpected risk of the prophylactic use of these drugs in sports.
- In our study, the role of confounders, as preexisting joint pain, could not be excluded.

**Abstract**

**Objectives:** To prevent pain inhibiting their performance, many athletes ingest over-the-counter (OTC) analgesics before competing. We aimed at defining the use of analgesics and the relation between OTC analgesic use/dose and adverse events (AEs) during and after the race, a relation that has not been investigated to date.

**Design:** Prospective (non-interventional) cohort study, using an on-line questionnaire

**Setting:** The Bonn marathon 2010

**Participants:** 3,913 out of 7,048 participants in the Bonn marathon 2010 returned their questionnaires.

**Primary and secondary outcomes:** Intensity of analgesic consumption before sports; Incidence of adverse events in the cohort of analgesic users as compared to non-users.

**Results:** There was no significant difference between premature race withdrawal rate in the analgesics cohort and the cohort who did not take analgesics ('controls'). However, race withdrawal because of gastrointestinal (GI) AEs was significantly more frequent in the analgesics cohort than in the control. Conversely, withdrawal because of muscle cramps was rare, but significantly more frequent in controls. The analgesics cohort had an almost ten times higher incidence of AEs (overall risk difference 13%). This incidence increased significantly with increasing analgesic dose. Nine respondents reported temporary ~~hospital admittance~~ **hospitalisation**: three for temporary kidney failure (post ibuprofen ingestion), four with bleeds (post aspirin ingestion), and two cardiac infarctions (post aspirin ingestion). None of the control reported ~~hospital admittance~~ **hospitalisation**.

**Conclusions:** The use of analgesics before participating in endurance sports may cause many, potentially serious, unwanted AEs that increase with increasing analgesic dose. Analgesic use before endurance sports appears to pose an unrecognized medical problem as yet. If verifiable in other endurance sports, it requires the attention of physicians and regulatory authorities.

## Introduction

Endurance sports are becoming increasingly popular. However, recent research has shown that physical activity does not automatically result in better health, but could exacerbate cardiovascular (CV) disease[1 2]. This may be related to the inhibition of cyclooxygenases by non-steroidal [anti](#)-inflammatory drugs (NSAIDs), including 'over the counter' (OTC) analgesics, that are known to exacerbate atherosclerosis[3] and CV problems in some patients[4].

Previous studies have shown that the use and abuse of analgesics in sports is frequent and possibly dangerous[5-11], and that the incidence and severity of electrolyte disturbances[12 13], gastrointestinal (GI)[14], and renal adverse events (AEs)[15-17] during and after racing double after taking analgesics. However, these studies investigated AEs in isolation and did not investigate a dose response relationship.

In a preliminary study, we interviewed 1,024 participants of the Bonn marathon/half marathon, and collected information on their training, fitness, and drug use<sup>[5]</sup>. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice<sup>[5]</sup>. These results were confirmed by Gorski et al[18].

We now report a follow-up study aiming at defining the use of analgesics in relation to premature race withdrawal, and AEs occurring during and after racing. [In this report, we summarize NSAIDs and other cyclooxygenase-inhibitors including acetaminophen \(paracetamol\) as analgesics.](#)

## Methods

### Study population

The investigation relied on a questionnaire made available to all participants of the Bonn marathon/half marathon 2010 on paper and via the internet by the organizer together with information on the purpose of the investigation. Participating in the study was recommended by the organizer (Figure S1). The questionnaire examined:



1. Background epidemiology: age, sex, running experience, use of analgesics during training/in previous races, and details of previous training.
2. Medication use before the race: name and dose of drugs taken before the race start, and any medical advice received.
3. During and after racing: completion/reasons for premature withdrawal from the race, and AEs.

### Study design

The study was conducted according to the Declaration of Helsinki on biomedical research involving human subjects (Somerset West amendment). Advertisement and study information was provided by the local organizer. All questionnaires returned were in an anonymised form which made identification of single participants impossible. The integrity of the participants remained unimpaired. After having consulted the local ethics committee, it was agreed that a formal application to the Institutional Ethics Review Board (IRB) was not required according to professional regulations. The scientific quality of the study design was not subjected to the control of the IRB.

The case reports (serious cases) were regarded as request for medical advice and handled as such by MK (MD) who preserved the anonymity of these “patients”.

All data sheets (received questionnaires) were checked for completeness and duplicates using SPSS software version 19, followed by inspection by two researchers.

### Outcome measures

The primary hypothesis was that consumption of analgesics is associated with an increased incidence of AEs. An AE was included in the analysis if one or more of the following events were recorded on the questionnaire: GI cramps and bleeds, haematuria, or CV events (e.g. arrhythmia, palpitation).

### Statistical analysis

AEs and reasons for premature race withdrawal were tabulated according to a number of population-based factors which may influence drug use or AE incidence. Cross-tables, the chi square test, or Fisher’s test were used to analyse subgroups to

1  
2  
3 establish relative risk differences and possible confounding factors. Drug doses (no  
4 drug, low dose, and high dose) were used to determine possible dose-related effects  
5 on AE incidence and race withdrawal.  
6  
7

8  
9 A binary regression model was used to estimate odds ratios and 95% confidence  
10 intervals for AE incidence in subgroups and in the primary study population, with  
11 adjustment for confounding factors. Analyses were conducted using SPSS software  
12 version 19. Statistical tests were two-sided, and p-values less than 0.05 were  
13 considered statistically significant. AEs from respondents who did not state which  
14 race they entered were not included in the marathon/half marathon sub-group  
15 analysis.  
16  
17  
18  
19

## 20 21 **Results**

22  
23 4,268 completed questionnaires were returned. More than 90% of the questionnaires  
24 were received by day 10, the rest within day seventeen after the race. Approximately  
25 4% were identified as duplicates, and were excluded from the analysis (Figure 1). An  
26 additional 4% of questionnaires were excluded because primary data were missing  
27 (i.e. age, sex, drug use, AEs).  
28  
29

30  
31  
32 The remaining 3,913 completed questionnaires constituted the primary study  
33 population, representing 56% of the participants in the Bonn marathon/half marathon  
34 2010 (Figure 1). Nearly half of the study cohort used analgesic before the actual race  
35 ('analgesic cohort': n=1931, 49%) and 51% reported not to have used any analgesic  
36 ('control group': n=1982; Figure 1).  
37  
38  
39

## 40 41 Background epidemiology

42  
43 Descriptive epidemiological data are given in Table S1 (supplementary information).  
44 Overall, there were more men than women (2,376 vs. 1,537), and men were slightly  
45 older on average (means  $\pm$ SD: 40  $\pm$ 10 vs. 39  $\pm$ 11 years). Males and females were  
46 younger in the control group (means  $\pm$ SD analgesic group: male 43  $\pm$ 8, female 42  $\pm$ 8  
47 years vs. control group: male 38  $\pm$ 12, female 34  $\pm$ 13 years). Most respondents had  
48 previous marathon experience (overall 87%). In the analgesics cohort, 20% had also  
49 taken analgesics during training (male 26% vs. female 14%), compared with 1% of  
50 the control group. Of the analgesics cohort, 11% recorded pain before the race  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 (compared with 1% of controls), and 16% recorded AEs during/after racing  
4 (compared with 2% of controls).  
5  
6

### 7 Medication use before racing

8  
9  
10 In total, 1,931 respondents ingested analgesics before racing, to retard or avoid pain  
11 during the races and thereafter. They used analgesics immediately before the race.  
12 Most of the analgesics (54%) were taken without prescription (Table S2), and  
13 significantly more women (61%) took analgesics than men (42%).  
14  
15

16  
17 The most frequently used analgesic was diclofenac, used by 47% of the analgesics  
18 cohort before the race (Table S2). Many athletes (11%) resorted to supra-OTC doses  
19 of diclofenac (over 100 mg). The second most commonly used analgesic was  
20 ibuprofen, and 43 % of those who took ibuprofen ingested  $\geq 800$  mg (twice as the  
21 recommended OTC single dose). Aspirin was used less frequently, and mostly at low  
22 therapeutic doses. Acetaminophen, celecoxib, dipyron, etoricoxib, meloxicam, and  
23 naproxen were also used, although these drugs were taken by comparatively few  
24 athletes and are grouped as 'other analgesics' in the analysis (Table S2).  
25  
26

27  
28 Of all respondents, 93% declared that they were not informed about the risks of using  
29 analgesics in connection with sports endurance (Table S1).  
30  
31

### 32 Events during and after the race:

33  
34  
35 The incidence of reported AEs was significantly higher in runners of the full marathon  
36 compared with the half-marathon (18% vs 7%;  $p < 0.001$ ). Additionally, the analgesic  
37 related AE risk in the full marathon cohort was significantly higher than in the half  
38 marathon cohort (odds 9.04; 95% CI 5.31-15.39 vs 3.20; CI 2.32-4.42. Figure 2).  
39  
40

41  
42 There were similar numbers of half marathon and marathon runners in the analgesics  
43 cohort compared with controls.  
44  
45

46  
47 A four to ten times higher incidence of each type of AE was observed in the  
48 analgesics cohort compared with controls (overall incidence 16% vs 4%. Table S3,  
49 Figure 3), with a calculated risk difference of 13%. The difference in the incidence of  
50 AEs between the two cohorts was most prominent with respect to GI cramps and CV-  
51 events (after race). In the analgesics cohort, GI cramps were the most frequent AE  
52 (reported by 14% of the cohort), followed by CV AEs after the race (9%). In the  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 controls, CV AEs after the race were the most frequently reported AE (3%, Table S3).  
4 Notably, haematuria was reported only in the analgesics cohort. The differences in  
5 the incidence of all AEs were highly significant between the two groups ( $p < 0.001$ ,  
6 Table S3, Figure 3).  
7  
8

9  
10 No significant difference was found between the analgesics cohort and controls in  
11 terms of premature race withdrawal overall (Table S3,  $p = 0.237$ ). Race withdrawal  
12 because of muscle cramps occurred significantly more often in controls (3% vs 1%,  
13 Table S3, Figure 4,  $p < 0.001$ ), but the absolute difference was small. Conversely,  
14 intestinal cramps were significantly more frequently blamed for race withdrawal in the  
15 analgesics cohort compared with controls (2% vs 1%;  $p < 0.01$ , Table S3, Figure 4).  
16  
17

18 Joint and muscle pain after the race were significantly more frequent in the  
19 analgesics cohort than in controls (1,301 vs 955 respondents,  $p < 0.001$ , Table S3,  
20 Figure 5).  
21

22 The overall risk for analgesic related AEs was estimated at 5.1 (95% CI 3.9-6.7;  
23  $p < 0.001$ , Figure 6), giving a 'number needed to harm' of eight treated participants. In  
24 a subsequent subgroup analysis for sex, age, training, marathon/half marathon run,  
25 and analgesic experience, an enhanced risks (odds ratio) for the different subgroups  
26 was detected, but this was very variable (1.6-13.4, Figure 2). Therefore, these  
27 subgroup parameters were included in a regression analysis which resulted in a  
28 comparable adjusted analgesic related risk of 3.0 (95% CI 2.1-4.1;  $p < 0.001$ , Figure  
29 6).  
30  
31

32 To investigate if the incidence of AEs was dose-dependent, a risk estimation of the  
33 size of the dose was conducted. The high dose resulted in a significantly higher risk  
34 of AEs compared with the lower dose or controls. Even the low dose group presented  
35 a higher risk of AEs compared with controls (Figure 6). This further adjusted  
36 regression model showed a statistically significant increased risk at rising doses,  
37 meaning that increasing the dose can increase the risk of AEs by three times (odds  
38 ratio 3.2; 95% CI, 2.7-4.0,  $p < 0.001$ , Figure 6).  
39  
40

41 Finally, the association of analgesic use with distinct side effect profiles was  
42 analysed. The ingestion of all three drugs used most frequently (aspirin, diclofenac,  
43 and ibuprofen) was associated with AEs in a dose-dependent manner (Table 1).  
44  
45

46 Overall, the "drug related" incidence (defined as the percentage of respondents  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 reporting AEs out of the total number of respondents taking a particular analgesic)  
4 was highest with aspirin, followed by ibuprofen, and lowest with diclofenac in both  
5 subgroups (high and low dose of analgesics—; Table 1). At high doses, 10% of  
6 diclofenac users, 52% of ibuprofen users, and 87% of aspirin users experienced AEs  
7 (Table 1). Aspirin was associated with relatively numerous GI or kidney bleeds,  
8 compared with the other analgesics (reported by 49% of the “high dose” Aspirin  
9 users).

### 10 11 12 **Serious cases**

13  
14  
15  
16  
17  
18 In addition to the evaluation by questionnaire, the participants of the Bonn  
19 marathon/half marathon 2010 were encouraged to report serious events which  
20 required hospital admittancehospitalisation during the 3 days following the race to the  
21 physician in charge, this evaluation (MK). Nine case reports of hospital  
22 admittancehospitalisation were received (Table S4 by MK), all of which concerned  
23 participants of the analgesics cohort. Three athletes (numbers 1-3, Table S4)  
24 reported anuria/oliguria which started the day after the race and lasted for up to three  
25 days. In two cases this AE resolved after a hyperuric period, and one respondent  
26 reported ongoing renal problems (haematuria for 2 days - number 3, Table 5). In all  
27 three cases, moderate doses of ibuprofen (2 x 400 mg, 600 mg, and 600 mg) were  
28 taken before and during the race together with large amounts of fluid.

29  
30  
31  
32  
33  
34  
35  
36  
37 Four respondents (numbers 4-7, Table S4) reported hospital  
38 admittancehospitalisation because of GI-bleeding (black stools and vomiting blood).  
39 Gastroendoscopic evaluation revealed at least one intervention requiring bleeding  
40 ulcer. The patientsThey were further monitoredtreated endoscopically and given  
41 proton pump inhibitors. All four respondents had ingested moderate amounts of  
42 aspirin (500-1,000 mg) before the race, and all were released after a few days  
43 without obvious sequelae.

44  
45  
46  
47  
48  
49 Two more respondents (numbers 8 and 9, Table S4) were hospitalised after ingesting  
50 aspirin before the race. One took a 100 mg dose to prevent infarction, the other took  
51 500 mg because of mild foot pain. Both respondents complained of chest pain,  
52 angina, and arrhythmia the day after racing, and both suffered cardiac infarctions.  
53 Both athletes recovered, although some cardiac damage remained in one  
54 respondent.

1  
2  
3 These nine cases are well documented (Table S4). However, it should be noted that  
4 since reporting was spontaneous and voluntary, and a lack of corresponding hospital  
5 admittance~~hospitalisation~~ in the control cohort could not be proven. Also we do not  
6 know if the patients/participants filled and submitted an (anonymized) questionnaire.  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Discussion

It is known that many professional and amateur athletes use analgesics prophylactically to increase performance and prevent pain[6-17 19 20].

A recent publication in the NEJM[12] warned that over-hydration during marathons might increase the risk of CV events. However, this study did not investigate the association between the use of drugs and CV problems. Recently, we reported that two-thirds of the participants of a marathon took analgesics before the start[21]. This investigation showed that most athletes taking analgesics had taken supra-therapeutic doses. Similar data were reported by Gorski et al[18]. However, these studies did not investigate the use of analgesics and premature race withdrawal, nor did they systematically record performance and incidence of AEs.

The current study was designed to test the hypothesis that cyclooxygenase inhibitors contribute to the development of AEs, which is possible since these drugs block the protective effects of prostaglandins on GI, CV, and renal function. We hypothesize that their use is likely to suspend the mucosa- and kidney-protective[3] effects of PGE<sub>2</sub>/PGI<sub>2</sub>, thus augmenting the damaging effect of diminished blood flow[22] and oxygen supply for the GI mucosa and kidney[23]. Moreover, it was postulated that marathon runs could decrease the barrier function of the intestinal mucosa, further increasing the absorption of bacterial toxins from the gut[24], and that repeated inhibition of the production of endothelium-produced PGI<sub>2</sub> during CV stress, e.g. intensive exercise, may accelerate atherosclerosis[1 2 25].

This study analysed respondents for age, sex, training status, drug use (including doses), race completion, and AEs that occurred during the race and afterwards. To the best of our knowledge, this study shows for the first time that the administration of analgesics before a marathon/half-marathon can significantly increase AEs, and these increase with increasing analgesic dose. This increased incidence of AEs is dramatic; e.g. 4% of respondents in the analgesics cohort reported haematuria compared with 0% of controls. Moreover, nine respondents reported [hospital admittance](#) caused by either temporary kidney failure, bleeding ulcers, or cardiac infarctions. All these serious events occurred in the analgesics cohort.

Altogether, these data do not support the contention that taking analgesics before racing improves the ability to complete the race or to prevent AEs thereafter.



Four aspects of this study deserve an in-depth discussion.

1. *Analgesics taken prophylactically before racing do not prevent pain*

Analysis of the pain reported by respondents before and after racing showed no major identifiable advantages gained from taking analgesics. Muscle cramps were reported as a reason for premature race withdrawal marginally less frequently in the analgesics cohort compared with the control. Although the difference was significant ( $p < 0.001$ ), the small sample size does not allow concrete conclusions to be drawn, particularly in the context of the parameters of overall pain during racing and intestinal cramps. There were significantly more intestinal cramps in the analgesics cohort ( $p < 0.001$ ) compared with the control, and more muscle and joint pain were reported in the analgesics cohort after racing than in the control.

This result supports observations reported by Nieman *et al.*, who found that the intake of ibuprofen at regular intervals during an ultra-marathon race did not decrease muscle soreness in the days afterwards[26]. This may be explained by the fact that all the drugs investigated (diclofenac, ibuprofen, and aspirin) display a short elimination half-life of around two hours, which would make effects several hours after the ingestion of the drugs rather unlikely. In the report by Nieman *et al.*, the last dose of ibuprofen was taken several hours before finishing the race, and so the lack of influence on post-race pain is not surprising. Several research groups have reported the analgesic effects of NSAIDs in volunteers undertaking physical exercise. However, in these studies, the drugs were given after exercise, not before, which makes their reported analgesic effect plausible and recognisable[27-29].

In conclusion, our data indicate that the intake of cyclooxygenase inhibitor analgesics does not offer protection from pain during or after a marathon/half marathon compared with controls. However definitive proof of this contention would warrant a prospective, randomised cohort study.

2. *Analgesics contribute to AEs*

This study investigated if cyclooxygenase inhibitors contribute to the AEs observed frequently in endurance sports[24 30]. All of the AEs observed



frequently during marathons, i.e. CV events, GI cramps/bleeds, and renal dysfunction, occurred much more frequently in the analgesics cohort compared with the control. This effect was not dependent on the type of analgesic, i.e. all three drugs used frequently caused an increase in CV, GI, and renal AEs. This supports our hypothesis that the use of cyclooxygenase inhibitors before the start of a race may be damaging because tissue protection that is usually provided by prostaglandins may be impaired, triggering GI, CV, and renal AEs. These effects again suggest that the use of cyclooxygenase inhibitors before and during a marathon/half marathon race may be dangerous and should be avoided.

### 3. *The AE profile of different analgesics is different*

Although the use of analgesics increases the overall incidence of AEs, all nine serious events reported to us which led to temporary [hospital admittance](#)~~hospitalisation~~ concur with the pattern of AEs seen per drug in the rest of the respondents. The three temporary kidney failure cases (all of whom had ingested ibuprofen) correspond with the relatively high incidence of renal AEs in the ibuprofen group (Table 1). Moreover, the bleeding ulcers observed in the aspirin group mirror the high incidence of GI problems seen after the intake of aspirin. Somewhat surprising is the fact that both cardiac infarctions occurred in the aspirin group. This is interesting since aspirin should have protected from such events. However, definite conclusions cannot be drawn because of the small sample size. Overall, our observations are in line with previous reports[1 31-33].

### 4. *Limitations of the study*

A double-blind, randomized, cross-over design for any trial is the gold standard. However, this is obviously impractical in these circumstances. Despite the relatively high return of questionnaires, there was still no information available for half of the marathon/half marathon participants, and many confounding factors such as BMI, use of other drugs etc. were not investigated. [Implementing a higher number of items in our questionnaire in order to cover additional confounders will have limited participant's compliance and the overall response rate.](#) Although the two cohorts were of similar sizes,

1  
2  
3 there are differences between them with respect to age, sex, training, and  
4 drug experience (a contribution of long term use of OTC analgesic on the  
5 incidence of AEs cannot be excluded), which may also have influenced the  
6 outcome. However, the considerable homogeneity of the AEs seen throughout  
7 all subgroups supports the overall contention that cyclooxygenase inhibitors  
8 taken before and during a marathon/half marathon race increase the risks of  
9 AEs substantially, without measurable benefit in terms of race completion.  
10  
11  
12  
13

14  
15 Taken together, our data indicate that the widespread use of cyclooxygenase  
16 inhibitors in connection with endurance sports is potentially damaging. In our study,  
17 the administration of analgesics before the start of a race did not prevent post-  
18 exercise pain or significantly reduce the premature withdrawal rate compared with the  
19 control. Conversely, the use of cyclooxygenase inhibitors considerably increased the  
20 incidence of GI, renal, and CV AEs. We conclude that the use of analgesics before  
21 and during endurance sports may pose a serious health problem that should be  
22 addressed. Our investigation has also shown a worrying lack of education about  
23 these AEs within the participants of the Bonn 2010 marathon/half marathon, which  
24 may highlight a larger problem if mirrored in the endurance sport community in  
25 general. We would encourage greater awareness of the possible AEs of these drugs,  
26 particularly among endurance sports enthusiasts.  
27  
28  
29  
30  
31  
32  
33  
34

35  
36 Further investigations are warranted to examine if the use of analgesics before and  
37 during sports activities should be avoided altogether.  
38  
39  
40  
41  
42

### 43 **Acknowledgements**

44  
45 K. Brune is Doerenkamp-Professor. He was supported by the Hertie Foundation.  
46 The authors declare no conflict of interest.  
47 The authors acknowledge the assistance of a medical writer in the editing and  
48 language checking of this manuscript.  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1: Incidence of [adverse events \(AEs\)](#) in relation to the analgesic used

Adverse events	Diclofenac n=913		Ibuprofen n=722		Aspirin n=141		Other analgesics n=175	
	Low dose n=693 <a href="#">#no. of reportse ases (%)</a> <sup>1</sup>	High dose n=220 <a href="#">no.# of reportse ases (%)</a>	Low dose n=410 <a href="#">no.# of reportse ases (%)</a>	High dose n=312 <a href="#">no.# of reportse ases (%)</a>	Low dose n=102 <a href="#">no.# of reportse ases (%)</a>	High dose n=39 <a href="#">no.# of reportse ases (%)</a>	Low dose n=107 <a href="#">no.# of reportse ases (%)</a>	High dose n=68 <a href="#">no.# of reportse ases (%)</a>
Urine blood	6 (1)	5 (2)	5 (1)	45 (14)	7 (7)	19 (49)	1 (1)	1 (2)
GI-cramp	16 (2)	5 (2)	52 (13)	89 (29)	11 (11)	9 (23)	4 (4)	9 (13)
GI-bleeding	2 (<1)	8 (4)	13 (3)	39 (13)	9 (9)	19 (49)	1 (1)	2 (3)
CV – during race	2 (<1)	0 (0)	40 (10)	28 (9)	3 (3)	8 (21)	5 (5)	0 (0)
CV – post race	4 (1)	8 (4)	44 (11)	97 (31)	11 (11)	12 (31)	3 (3)	3 (4)
Total (individuals) <sup>2</sup>	25	22	56	163	25	34	11	12
<a href="#">Drug related AE incidence</a>	<a href="#">4%</a>	<a href="#">10%</a>	<a href="#">14%</a>	<a href="#">52%</a>	<a href="#">25%</a>	<a href="#">34%</a>	<a href="#">11%</a>	<a href="#">12%</a>

<sup>1</sup> ~~Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.% relative to the size of the group. Percentages rounded to the nearest whole number.~~

<sup>2</sup> Number of individuals reporting AEs (a single individual may report >1 AE)

See Table [S2](#) for definition of dose sizes

**References:**

1. Schwartz JG, Merkel-Kraus, S., Duval, S., Harris, K., Peichel, G., Lesser, J.R., Knickelbine T., Flyngenring, B., Longe, T.R., Pastorius, C., Roberts, W.R., Oesterle, S.C., Schwartz, R.S. Does longterm endurance running enhance or inhibit coronary artery plaque formation? A prospective multidetector CTA study of men completing marathons for least 25 consecutive years. *J Am Coll Cardiol* 2010;**55**(10A):A.173.E1624
2. Mohlenkamp S, Lehmann N, Breuckmann F, et al. Running: the risk of coronary events : Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J* 2008;**29**(15):1903-10 doi: 10.1093/eurheartj/ehn163[published Online First: Epub Date]].
3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol* 2011;**31**(5):986-1000 doi: 10.1161/ATVBAHA.110.207449[published Online First: Epub Date]].
4. Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;**368**(9549):1771-81 doi: 10.1016/S0140-6736(06)69666-9[published Online First: Epub Date]].
5. Brune K, Niederweis U, Krämer B. Sport und Schmerzmittel: Unheilige Allianz zum Schaden der Niere. *Deutsches Ärzteblatt* 2008;**105**(37):1894-900
6. Tscholl P, Alonso JM, Dolle G, Junge A, Dvorak J. The use of drugs and nutritional supplements in top-level track and field athletes. *Am J Sports Med* 2010;**38**(1):133-40 doi: 10.1177/0363546509344071[published Online First: Epub Date]].
7. Tscholl P, Feddermann N, Junge A, Dvorak J. The use and abuse of painkillers in international soccer: data from 6 FIFA tournaments for female and youth players. *Am J Sports Med* 2009;**37**(2):260-5 doi: 10.1177/0363546508324307[published Online First: Epub Date]].
8. 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[published Online First: Epub Date]].
9. Taioli E. Use of permitted drugs in Italian professional soccer players. *Br J Sports Med* 2007;**41**(7):439-41 doi: 10.1136/bjism.2006.034405[published Online First: Epub Date]].
10. Alaranta A, Alaranta H, Heliovaara M, Airaksinen M, Helenius I. Ample use of physician-prescribed medications in Finnish elite athletes. *Int J Sports Med* 2006;**27**(11):919-25 doi: 10.1055/s-2006-923811[published Online First: Epub Date]].
11. Da Silva ER, De Rose EH, Ribeiro JP, et al. Non-steroidal anti-inflammatory use in the XV Pan-American Games (2007). *Br J Sports Med* 2011;**45**(2):91-4 doi: 10.1136/bjism.2009.065342[published Online First: Epub Date]].
12. Almond CS, Shin AY, Fortescue EB, et al. Hyponatremia among runners in the Boston Marathon. *N Engl J Med* 2005;**352**(15):1550-6 doi: 10.1056/NEJMoa043901[published Online First: Epub Date]].
13. Wharam PC, Speedy DB, Noakes TD, Thompson JM, Reid SA, Holtzhausen LM. NSAID use increases the risk of developing hyponatremia during an Ironman triathlon. *Med Sci Sports Exerc* 2006;**38**(4):618-22 doi: 10.1249/01.mss.0000210209.40694.09[published Online First: Epub Date]].
14. Halvorsen FA, Lyng J, Ritland S. Gastrointestinal bleeding in marathon runners. *Scand J Gastroenterol* 1986;**21**(4):493-7
15. Le Meur Y, Paraf F, Szelag JC, Aldigier JC, Leroux-Robert C. Acute renal failure in a marathon runner: role of glomerular bleeding in tubular injury. *Am J Med* 1998;**105**(3):251-2

16. Irving RA, Noakes TD, Raine RI, Van Zyl Smit R. Transient oliguria with renal tubular dysfunction after a 90 km running race. *Med Sci Sports Exerc* 1990;**22**(6):756-61
17. Boulter J, Noakes TD, Hew-Butler T. Acute renal failure in four Comrades Marathon runners ingesting the same electrolyte supplement: coincidence or causation? *S Afr Med J* 2011;**101**(12):876-8
18. Gorski T, Cadore EL, Pinto SS, et al. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med* 2011;**45**(2):85-90 doi: 10.1136/bjsm.2009.062166[published Online First: Epub Date] | .
19. Doraiswamy PM, Hoffman B.M. Fitness and the Brain: Can a Walk a Day Keep Alzheimer's Away? *Scientific American* 2008;**4**
20. Lippi G, Franchini M, Guidi GC, Kean WF. Non-steroidal anti-inflammatory drugs in athletes. *Br J Sports Med* 2006;**40**(8):661-2; discussion 62-3 doi: 10.1136/bjsm.2006.027342[published Online First: Epub Date] | .
21. Brune K, Niederweis U, Kaufmann A, Kuster-Kaufmann M. [Drug use in participants of the Bonn Marathon 2009]. *MMW Fortschr Med* 2009;**151**(40):39-41
22. Kehl O, Jager K, Munch R, et al. [Mesenterial anemia as a cause of jogging anemia?]. *Schweiz Med Wochenschr* 1986;**116**(29):974-6
23. Noakes TD, Sharwood K, Speedy D, et al. Three independent biological mechanisms cause exercise-associated hyponatremia: evidence from 2,135 weighed competitive athletic performances. *Proc Natl Acad Sci U S A* 2005;**102**(51):18550-5 doi: 10.1073/pnas.0509096102[published Online First: Epub Date] | .
24. Pals KL, Chang RT, Ryan AJ, Gisolfi CV. Effect of running intensity on intestinal permeability. *J Appl Physiol* 1997;**82**(2):571-6
25. Scott PA, Kingsley GH, Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. *Eur J Heart Fail* 2008;**10**(11):1102-7 doi: 10.1016/j.ejheart.2008.07.013[published Online First: Epub Date] | .
26. Nieman DC, Henson DA, Dumke CL, et al. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Brain Behav Immun* 2006;**20**(6):578-84 doi: 10.1016/j.bbi.2006.02.001[published Online First: Epub Date] | .
27. Tokmakidis SP, Kokkinidis EA, Smilios I, Douda H. The effects of ibuprofen on delayed muscle soreness and muscular performance after eccentric exercise. *J Strength Cond Res* 2003;**17**(1):53-9
28. Hasson SM, Daniels JC, Divine JG, et al. Effect of ibuprofen use on muscle soreness, damage, and performance: a preliminary investigation. *Med Sci Sports Exerc* 1993;**25**(1):9-17
29. Donnelly AE, McCormick K, Maughan RJ, Whiting PH, Clarkson PM. Effects of a non-steroidal anti-inflammatory drug on delayed onset muscle soreness and indices of damage. *Br J Sports Med* 1988;**22**(1):35-8
30. Lambert GP, Boylan M, Laventure JP, Bull A, Lanspa S. Effect of aspirin and ibuprofen on GI permeability during exercise. *Int J Sports Med* 2007;**28**(9):722-6 doi: 10.1055/s-2007-964891[published Online First: Epub Date] | .
31. Robertson JD, Maughan RJ, Davidson RJ. Faecal blood loss in response to exercise. *Br Med J (Clin Res Ed)* 1987;**295**(6593):303-5
32. Simons SM, Kennedy RG. Gastrointestinal problems in runners. *Curr Sports Med Rep* 2004;**3**(2):112-6
33. Page AJ, Reid SA, Speedy DB, Mulligan GP, Thompson J. Exercise-associated hyponatremia, renal function, and nonsteroidal antiinflammatory drug use in an ultraendurance mountain run. *Clin J Sport Med* 2007;**17**(1):43-8 doi: 10.1097/JSM.0b013e31802b5be9[published Online First: Epub Date] | .

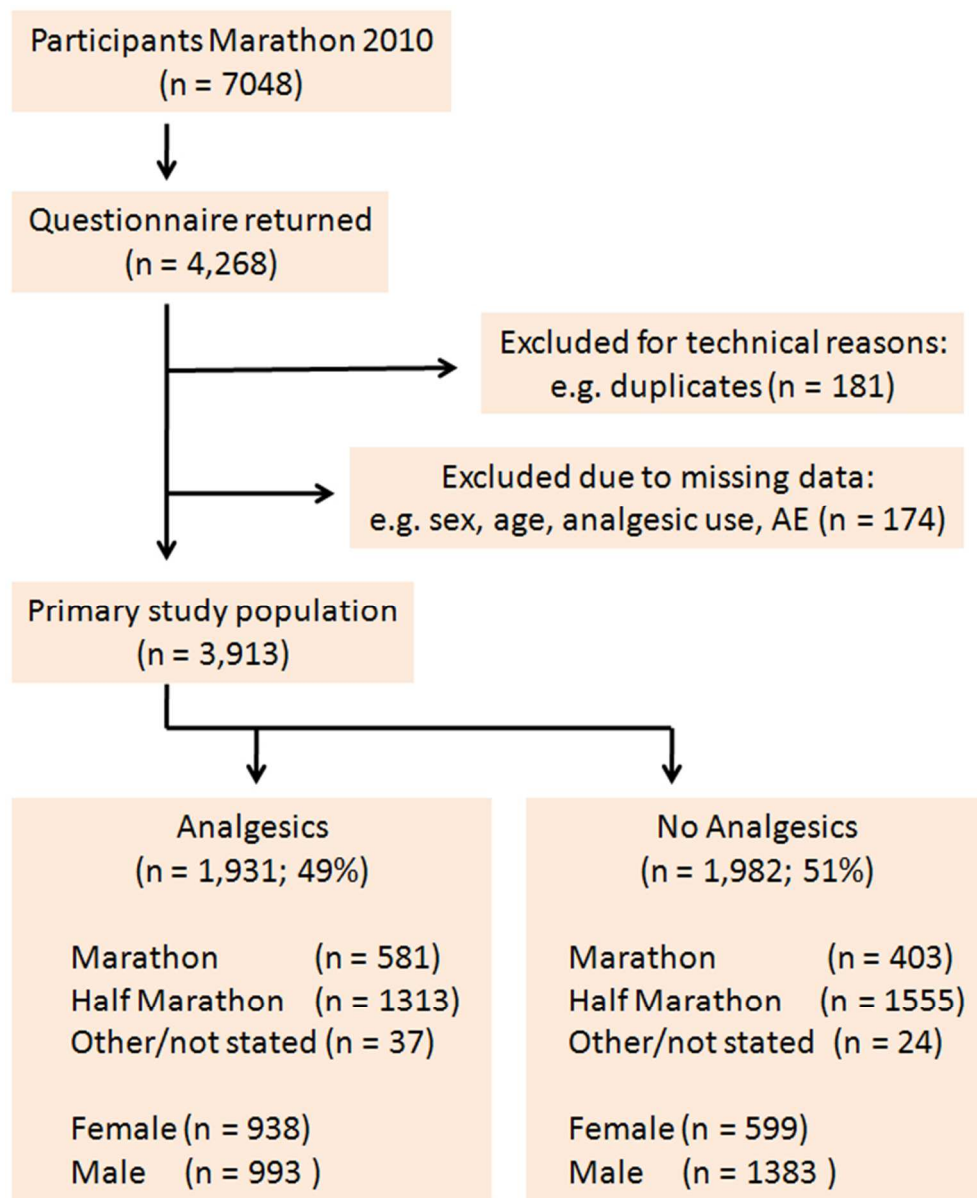


Figure 1: Flow chart of the evaluation of the marathon/half marathon running cohort. After the elimination of duplicates, almost 2,000 questionnaires were returned from each cohort. The distribution of marathon and half-marathon runners was similar in each treatment cohort. If participants entered races other than the marathon or half marathon (e.g. relays), or did not state which race they entered, they were captured in the 'other/not stated' cohort (AE; adverse event).  
56x68mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

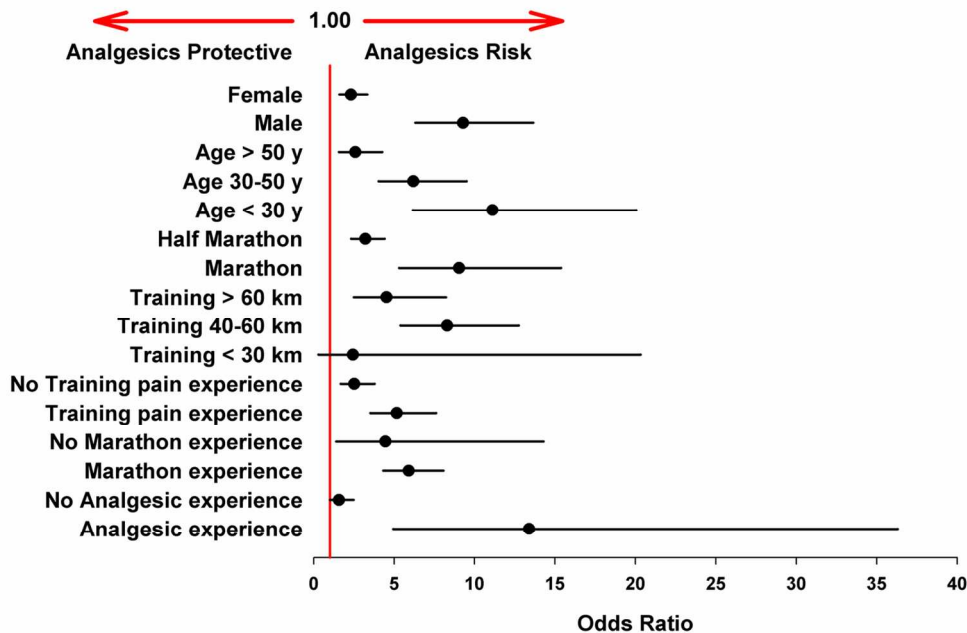


Figure 2: Risk of adverse events (AEs) within study subgroups (unadjusted). Odds ratios were estimated by binary linear regression analysis. Almost all subgroups show enhanced risk for AEs after analgesic use (odds ratios >1; error bars represent CI95%).  
124x79mm (300 x 300 DPI)

view only



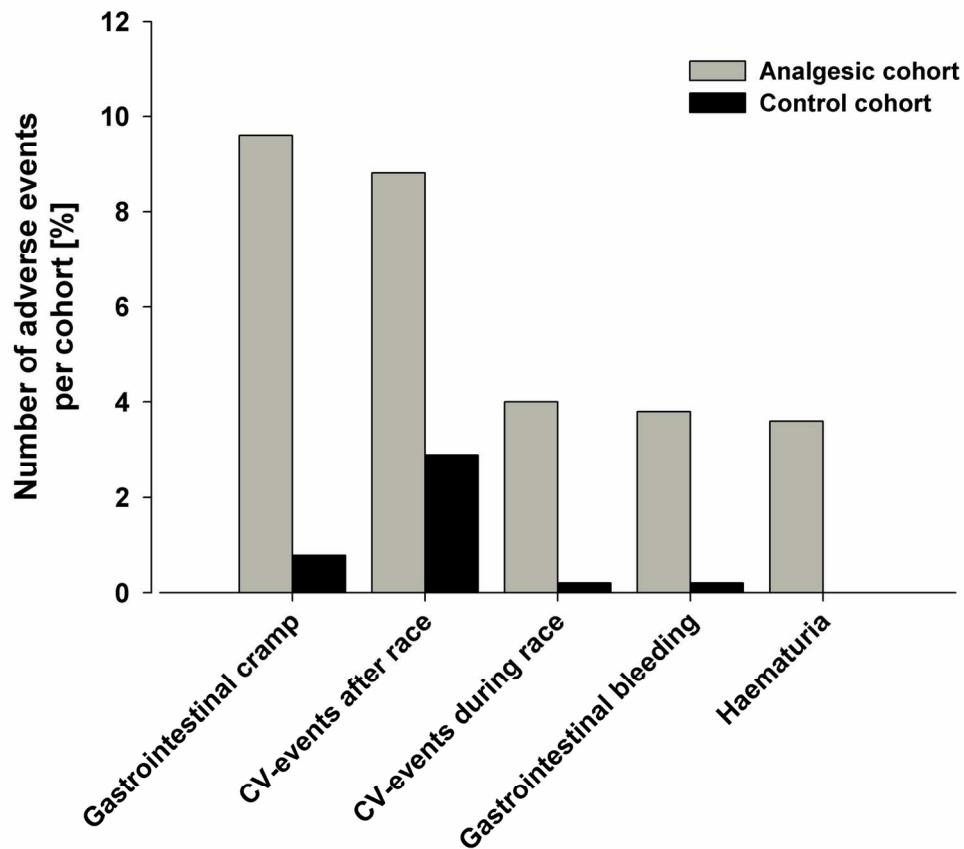


Figure 3: Incidence of adverse events (AEs, derived from Table S3)  
Rounded percentages are given in Table S3  
The differences between the groups were all highly significant;  $p < 0.001$ .  
150x144mm (300 x 300 DPI)



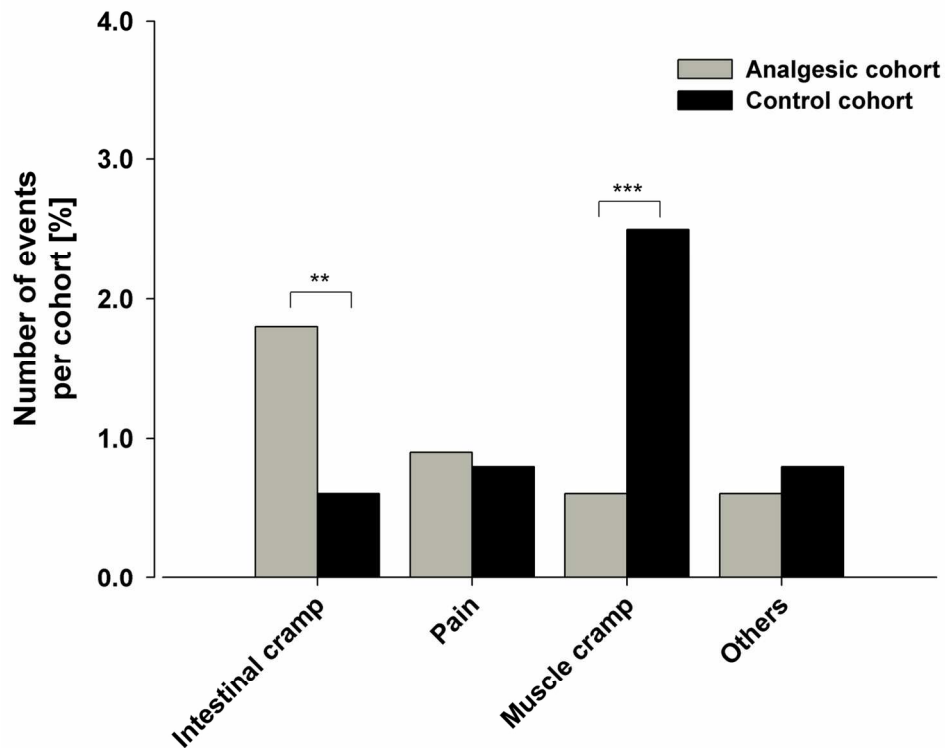


Figure 4: Reasons for premature termination of the race.  
 Rounded percentages are given in Table S3

\*\*p<0.01

\*\*\*p<0.001

Note: the absolute numbers are small.  
 137x117mm (300 x 300 DPI)

only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

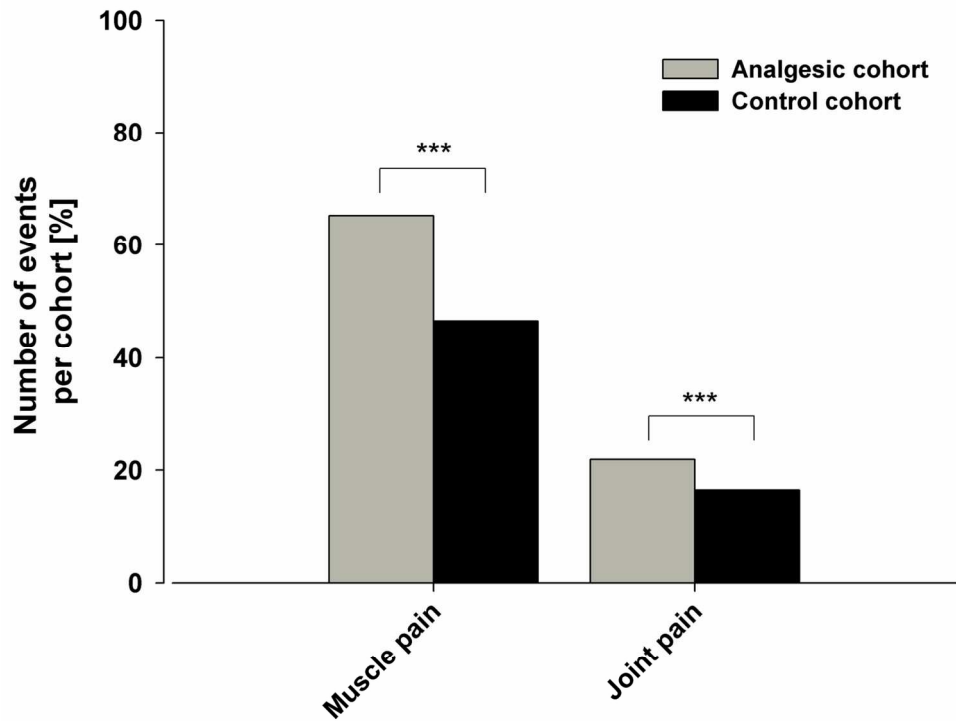


Figure 5: Percentage of runners experiencing muscle and/or joint pain after the race.  
Rounded percentages are given in Table S3  
The differences are highly significant (\*\*\*) p < 0.001.  
131x108mm (300 x 300 DPI)

only

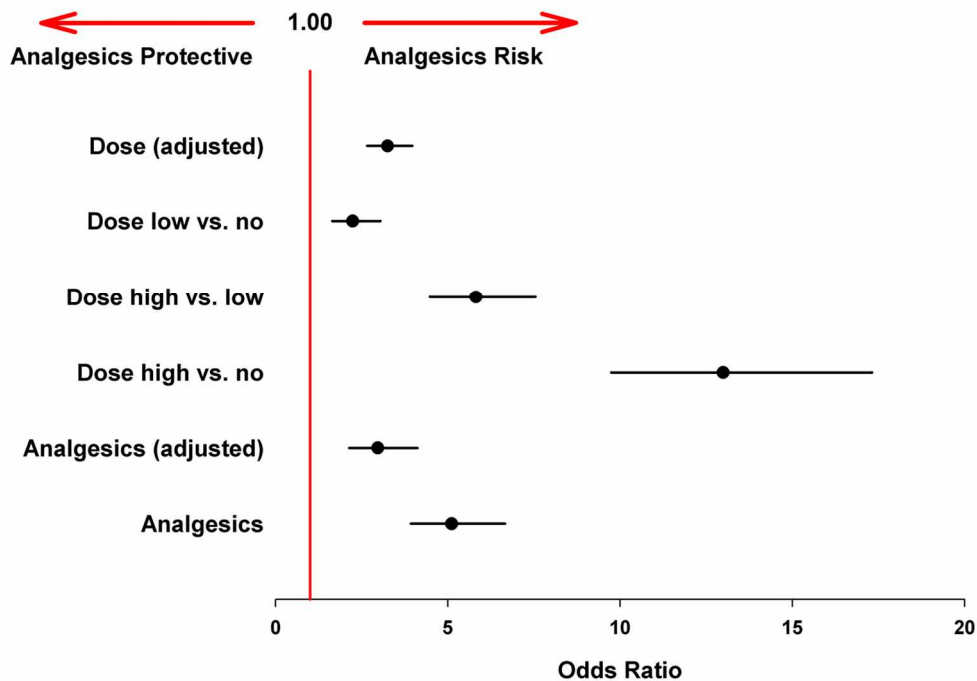


Figure 6: Adjusted adverse event (AE) risks for analgesic use and dose dependency  
 There was a significant dose/AE relationship and reported odds ratios increased with increasing dose differences (Dose no = controls without analgesic use). Adjusted odds ratios were estimated by binary linear regression using possible confounders (error bars represent CI95%).  
 124x85mm (300 x 300 DPI)

**Bonn Marathon – Questionnaire for all sportsmen (2010)**

Participant number ..... (voluntary) to avoid double registration; anonymity assured!

1) Sex  female /  male

2)  non-professional or  professional athlete

3) Age (years) ..... J

4) Do have marathon experience?  yes /  no

5) Running performance/week within the last 3 months approximately .....km

6) Did you experience joint, muscle, or back pain during or after training?  yes /  no

7) Do you have experience with analgesics in connection with sport?  yes /  no

8) Did you ingest analgesics before today's marathon, such as diclofenac, aspirin, ibuprofen, naproxen, acetaminophen, dipyrone?

1. Did you take analgesics before the start?  yes /  no

2. Did you have pain before the start of today's marathon?  yes /  no

3. Which analgesic and which dose did you take?

Ibuprofen Please select...	Diclofenac Please select...	Aspirin Please select...
Naproxen Please select...	Meloxicam Please select...	Celebrex Please select...
Etoricoxib Please select...	Acetaminophen Please select...	Dipyrone Please select...

Others: .....

4.  prescription or  OTC?

9) Do you use analgesic during training?  yes /  no

10) Did a physician check your laboratory values while preparing for the marathon (e.g. kidney lab values)?  yes /  no

11) Have you been informed about the risks of using analgesics in connection with a marathon?  yes /  no

12.) In which race did you participate:

a.  marathon,  half marathon,  relay (4 participants split the marathon distance)

b. Inline skating  full distance or  half distance

c. others: .....Km

13) During the race:

a. Hematuria  yes /  no

b. GI-cramps  yes /  no

c. GI-bleeds  yes /  no

d. CV-events (extrasystole, palpitation, tachycardia, and others)  yes /  no

14) After the race:

a. CV-events  yes /  no

b. Athralgia  yes /  no

c. Myalgia  yes /  no

15) I withdrew from the race for the following reason(s):

a.  I got tired of it

b.  I experienced severe pain

c.  I experienced GI-cramps

d.  I experienced muscle cramps

e.  other reasons: .....

Many thanks for your cooperation.

Dr. med. Michael Küster, Bonn, April 2010

[Send / transfer data...](#)

Figure S1: Questionnaire supplied to marathon/half marathon participants.  
103x68mm (300 x 300 DPI)

Table S1: Descriptive data on the participants

General information		Analgesics (49%)*			No Analgesics (51%)			Study population (100%)
		Female n=938	Male n=993	All** Female and Male n=1931	Female n=599	Male n=1,383	All** Female and Male n=1,982	Total n=3,913 # of cases
		no. of cases (%)#	no. of cases (%)	no. of cases (%)	no. of cases (%)	no. of cases (%)	no. of cases (%)	no. of cases (%)
Age	≤30 y	67 (7)	57 (6)	124 (6)	345 (58)	443 (32)	788 (40)	912 (23)
	>30, ≤50 y	724 (77)	789 (80)	1513 (78)	141 (24)	707 (51)	848 (43)	2361 (60)
	>50 y	147 (16)	147 (15)	294 (15)	113 (19)	233 (17)	346 (18)	640 (16)
Experience	amateur	916 (98)	980 (99)	1896 (98)	588 (98)	1,355 (98)	1943 (98)	3839 (98)
	professional	4 (<1)	2 (<1)	6 (<1)	6 (1)	17 (1)	23 (1)	29 (1)
Previous marathon experience	yes	927 (99)	974 (98)	1901 (98)	398 (66)	1,121 (81)	1,519 (77)	3420 (87)
Training per week last 3 months	<40 km	4 (<1)	4 (<1)	8 (<1)	345 (58)	286 (21)	631 (32)	639 (16)
	40-60 km	729 (78)	508 (51)	1237 (64)	135 (23)	769 (56)	904 (46)	2141 (55)
	>60 km	201 (21)	478 (48)	679 (35)	119 (20)	328 (24)	447 (23)	1126 (29)
Pain during training	yes	573 (61)	382 (39)	955 (50)	193 (32)	308 (22)	501 (25)	1456 (37)
Analgesic use during sport	yes	534 (57)	906 (91)	1440 (75)	33 (6)	189 (14)	222 (11)	1662 (43)
Analgesic use during training	yes	129 (14)	254 (26)	383 (20)	7 (1)	9 (1)	16 (1)	399 (10)
Pain immediately before the race	yes	160 (17)	48 (5)	208 (11)	9 (2)	13 (1)	22 (1)	230 (6)
Lab check <sup>1</sup>	yes	64 (7)	52 (5)	116 (6)	62 (10)	120 (9)	182 (9)	298 (8)
Information received on the risk of analgesics	yes	34 (4)	30 (3)	64 (3)	58 (10)	76 (6)	134 (7)	198 (5)
	no	889 (95)	936 (95)	1825 (95)	520 (87)	1273 (92)	1793 (91)	3618 (93)

Race entered	Marathon	147 (16)	434 (44)	581 (30)	48 (8)	355 (26)	355 (26)	984 (25)
	Half marathon	778 (83)	535 (54)	1313 (68)	545 (91)	1,010 (73)	1,010 (73)	2868 (73)
	Other/not stated	13	24	37	6	18	18	61 (2)
Adverse events	yes	133 (14)	179 (18)	312 (16)	40 (7)	32 (2)	32 (2)	384 (10)

\*Percentages relate to the primary study population, and rounded to the nearest whole number.

# Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

\*\*The difference of all parameters was significant ( $p=0.002$  to  $p<0.001$ ) when analgesic and control cohort were compared (chi square tests, Fishers tests and U-tests).

<sup>1</sup> Lab check; Laboratory parameters tested before the race (e.g. kidney values; see question 10 in Figure S1)

Table S2: Use of analgesics before the marathon/half marathon

Drugs	Doses	All n=1,931 no. of reports (%) <sup>1</sup>	Female n=938 no. of reports (%)	Male n=993 no. of reports (%)
Diclofenac	≥ 100 mg (high)	219 (11)	91 (10)	128 (13)
	≤ 75 mg / unknown (low)	694 (36)	317 (34)	377 (38)
	Total (individuals): None <sup>2</sup>	1,018	530	488
Ibuprofen	≥ 800 mg (high)	312 (16)	129 (14)	183 (18)
	≤ 600 mg / unknown (low)	410 (21)	217 (23)	193 (19)
	Total (individuals): None	1,209	592	617
Aspirin	≥ 750 mg (high)	13 (<1)	8 (<1)	5 (<1)
	≤ 500 mg / unknown (low)	128 (7)	59 (6)	69 (7)
	Total (individuals): None	1,790	871	919
Other analgesics <sup>3</sup>	High	68 (4)	44 (5)	24 (2)
	Low	107 (6)	70 (7)	37 (4)
	Total (individuals): None	1,756	824	932
	Prescribed	42 (2)	21 (2)	21 (2)
	OTC	1,041 (54)	132 (14)	909 (92)
	Missing (data not reported)	848 (44)	785 (84)	63 (6)

<sup>1</sup> Percentages: number of reports relate to the total number in the group, and rounded to the nearest whole number.

<sup>2</sup> Number of individuals reporting "None" in the 'analgesic cohort', given for comparison.

<sup>3</sup> Other analgesics high dose / low dose, naproxen >500 mg / ≤ 500 mg or unknown, meloxicam ≥ 15 mg / ≤ 7.5 mg or unknown, celecoxib ≥ 400 mg / ≤ 200 mg or unknown, etoricoxib ≥ 120 mg / ≤ 90 mg or unknown, acetaminophen ≥ 1000 mg / ≤ 500 mg or unknown, dipyrrone ≥ 1000 mg / ≤ 500 mg or unknown.

Table S3: Adverse events during and after the marathon/half marathon

Reports	Analgesics (49%)				No Analgesics (51%)			
	Half marathon n=1,313	Marathon n=581	Other /not stated n=37	All n=1,931	Half marathon n=1,555	Marathon n=403	Other /not stated n=24	All n=1,982
	no. of reports (%) <sup>1</sup>	no. of reports (%)	no. of reports (%)	no. of reports (%)	no. of reports (%)	no. of reports (%)	no. of reports (%)	no. of reports (%)
<b>AEs<sup>2</sup></b>								
Urine blood	23 (2)	41 (7)	5 (14)	69 (4)	0 (0)	0 (0)	0 (0)	0 (0)
GI-cramp	84 (6)	98 (17)	3 (8)	185 (10)	7 (1)	8 (2)	0 (0)	15 (<1)
GI-bleeding	22 (2)	46 (8)	6 (16)	74 (4)	0 (0)	3 (1)	0 (0)	3 (<1)
CV-during race	11 (1)	66 (11)	1 (3)	78 (4)	3 (<1)	1 (<1)	0 (0)	4 (<1)
CV-post race	47 (4)	112 (19)	11 (30)	170 (9)	49 (3)	8 (2)	1 (4)	58 (3)
Total (individuals) <sup>3</sup>	138	158	16	312	55	16	1	72
<b>Reasons for premature race withdrawal</b>								
Intestinal cramp	35 (3)	0 (0)	0 (0)	35 (2)	12 (1)	0 (0)	0 (0)	12 (1)
Pain	14 (1)	3 (1)	0 (0)	17 (1)	16 (1)	0 (0)	0 (0)	16 (1)
Muscle cramp	9 (1)	1 (<1)	1 (3)	11 (1)	47 (3)	3 (1)	0 (0)	50 (3)
Others	8 (1)	3 (1)	1 (3)	12 (1)	14 (1)	1 (<1)	0 (0)	15 (1)
Total (individuals) <sup>4</sup>	66	7	2	75	89	4	0	93
<b>Pain post exercise</b>								
Joint	119 (9)	290 (50)	14 (38)	423 (22)	179 (12)	143 (36)	5 (21)	327 (17)
Muscle	929 (71)	308 (53)	22 (59)	1,259 (65)	642 (41)	271 (67)	10 (42)	923 (47)
Total (individuals)	955	323	23	1,301	710	274	11	995

<sup>1</sup> Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

<sup>2</sup> The difference of the incidence of all AEs was highly significant ( $p < 0.001$ ) when the "all" groups were combined, details and significance ranges are given in Figure 3

<sup>3</sup> Number of individuals reporting AEs (a single individual may report >1 AE)

<sup>4</sup> The overall difference of withdrawals comparing the analgesic and control cohort was not significant ( $p = 0.237$ ; also compare Figure 4)



Table S4: Serious adverse events causing hospital admittance

No.	Drug (dose and time of intake)	Reason for intake	Patient (sex, age)	Symptoms (time after intake)	Diagnosis (means)	Therapy	Outcome
1	Ibuprofen (600 mg BS)	Fear of joint pain	Female, 38 years	Oliguria, dyspnoea	Haematuria, hyperkalaemia, proteinuria	Furosemide, fluid, electrolytes	Recovered
2	Ibuprofen (400 mg BS and 400 mg DR)	Unknown	Male, 47 years	Anuria, haematuria at day 2	Empty bladder	Furosemide	Recovered
3	Ibuprofen (600 mg BS)	Joint pain (former body-builder), impaired kidney function	Male, 57 years	Anuria, arrhythmia (RR 220/120 mmHg)	Anuria	Haemofiltration, electrolytes, furosemide for 10 days	Incompletely recovered
4	Aspirin (500 mg BS)	Dysmenorrhoea	Female, 28 years	Black stool at day 1	Bleeding gastric ulcer	Gastroscopic intervention, omeprazole	Recovered
5	Aspirin (500 mg BS)	Fear of joint pain	Male, 43 years	Vomiting (blood stained), GI-cramps at day 1, black stool	Toxic erosive gastritis	Omeprazole	Recovered
6	Aspirin (1000 mg BS)	Enhance performance	Male, 33 years	GI-cramps, vomiting (blood stained)	Haemorrhagic gastritis	Gastroscopy, pantozole	Recovered
7	Aspirin (1000 mg BS)	Joint pain	Male, 53 years	GI-cramps (evening), black stool	2 gastric ulcers	Gastroscopic intervention, omeprazole	Recovered
8	Aspirin (500 mg BS)	Foot pain	Male, 38 years (experienced in sports)	Chest pain during race	ECG: infarction (small)	No specific therapy	Recovered
9	Aspirin (100 mg; BS)	Fear of infarction	Male, 51 years (apparently healthy)	Chest pain	ECG, troponin test: (small) infarction	Intensive care, rehabilitation	Unknown

BS = before start of the race; DR = during race; ECG = electrocardiogram; RR = blood pressure

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.