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

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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.

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 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.

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 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[5-10], and that the incidence and severity of CV[11,12], gastrointestinal (GI)[13], and renal adverse events (AEs)[14-16] 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[5]. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice[5].

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

All data were submitted by internet or email, and were checked for completeness 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 drug, low dose, and high dose) were used to determine possible dose-related effects on AE incidence and race withdrawal.

A binary regression model was used to estimate odds ratios and 95% confidence intervals for AE incidence in subgroups and in the primary study population, with adjustment for confounding factors. Analyses were conducted using SPSS software version 19. Statistical tests were two-sided, and p-values less than 0·05 were considered statistically significant. AEs from respondents who did not state which race they entered were not included in the marathon/half marathon sub-group analysis.

Results

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

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

Background epidemiology

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

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

Medication use before racing

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

The most frequently used analgesic was diclofenac, used by 47% of the analgesics cohort before the race (Table 2). Many athletes (11%) resorted to supra-OTC doses of diclofenac (over 100 mg). The second most commonly used analgesic was ibuprofen, and 43 % of those who took ibuprofen ingested ≥ 800 mg (twice as the recommended OTC single dose). Aspirin was used less frequently, and mostly at therapeutic doses. Acetaminophen, celecoxib, dipyrone, etoricoxib, meloxicam, and naproxen were also used, although these drugs were taken by comparatively few athletes and are grouped as 'other analgesics' in the analysis (Table 2).

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

Events during and after the race:

The incidence of AEs was significantly higher in runners of the full marathon compared with the half-marathon (18% vs 7%; p<0·001). Additionally, the analgesic related AE risk in the full marathon cohort was significantly higher than in the half marathon cohort (odds 9·04; 95% CI 5·31-15·39 vs 3·20; CI 2·32-4·42. Figure 3).

There were similar numbers of half marathon and marathon runners in the analgesics cohort compared with controls. A four to ten times higher incidence of each type of AE was observed in the analgesics cohort compared with controls (overall incidence 4% vs 16%. Table 3, Figure 4), with a calculated risk difference of 13%. The difference in the incidence of AEs between the two cohorts was most prominent with respect to GI cramps and CV-events (after race). In the analgesics cohort, GI cramps were the most frequent AE (reported by 14% of the cohort), followed by (unspecified) CV AEs after the race (9%). In the controls, (unspecified) CV AEs after the race were the most frequently reported AE (3%, Table 3). Notably, haematuria occurred only in the analgesics cohort. The differences in the incidence of all AEs were highly significant between the two groups (p<0·001, Table 3, Figure 4).

No significant difference was found between the analgesics cohort and controls in premature race withdrawal overall (Table 3, p=0·237). Race withdrawal because of muscle cramps occurred significantly more often in controls (3% vs 1%, Table 3, Figure 5, p<0·001), but the absolute difference was small. Conversely, intestinal cramps were significantly more frequently blamed for race withdrawal in the analgesics cohort compared with controls (2% vs 1%; p<0·01, Table 3, Figure 5).

Joint and muscle pain after the race were significantly more frequent in the analgesics cohort than in controls (1,301 vs 955 respondents, p<0·001, Table 3, Figure 6).

The overall risk for analgesic related AEs was estimated at 5·1 (95% CI 3·9-6·7; p<0·001, Figure 7), giving a ‘number needed to harm’ of eight treated people. In a subsequent subgroup analysis for sex, age, training, marathon/half marathon run, and analgesic experience, an enhanced risks (odds ratio) for the different subgroups was detected, but this was very variable (1·6-13·4, Figure 3). Therefore, these subgroup parameters were included in a regression analysis which resulted in a comparable adjusted analgesic related risk of 3 0 (95% CI 2 1-4 1; p<0·001, Figure 7).

To investigate if the incidence of AEs was dose-dependent, a risk estimation of the size of the dose was conducted. The high dose resulted in a significantly higher risk 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

regression model showed a statistically significant increased risk at rising doses, meaning that increasing the dose can increase the risk of AEs by three times (odds ratio 3·2; 95% CI, 2 7-4 0, p<0·001, Figure 7).

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

Serious cases

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

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

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

angina, and arrhythmia the day after racing, and both suffered cardiac infarctions. Both athletes recovered, although some cardiac damage remained in one respondent.

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

Discussion

It is known that many professional and amateur athletes use analgesics prophylactically to increase performance and prevent pain[6-8,18].

A recent publication in the NEJM[11] 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. This investigation showed that most athletes taking analgesics had either taken unsuitable drugs or supra-therapeutic doses. However, the study did not investigate the use of analgesics and premature race withdrawal, nor did it 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 hypothesise that their use is likely to suspend the mucosa- and kidney-protective[3] effects of PGE_2/PGI_2, thus augmenting the damaging effect of diminished blood flow[19] and oxygen supply for the GI mucosa and kidney[20]. 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[21], and that repeated inhibition of the production of endothelium-produced PGI_2 during CV stress, e.g. intensive exercise, may accelerate atherosclerosis[1,2,22].

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 hospitalisation 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 ($p< 0{\cdot}001$), 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 ($p< 0{\cdot}001$) 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[23]. 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 a few 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[24-26].

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[21,27]. 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 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 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 5, Table 4). 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[1,28-30].

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. Although the two cohorts were of similar sizes, there are differences between them with respect to age, sex, training, and drug experience (a contribution of long term use of OTC analgesic on the incidence of AEs cannot be excluded), which may also have influenced the outcome. However, the considerable homogeneity of the AEs seen throughout all subgroups supports the overall contention that cyclooxygenase inhibitors taken before and during a marathon/half marathon race increase the risks of AEs substantially, without measurable benefit in terms of race completion.

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

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

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There is no additional data available.

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

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

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Competing Interests Statement: 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.

Data Sharing Statement: There is no additional data available.

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)
	profession al	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 immediatel y before the race	yes	160 (17)	48 (5)	208 (11)	9 (2)	13 (1)	22 (1)	230 (6)
Lab check[1]	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).
[1] 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 (%)[1]	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[2]	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[3]	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)

[1] Percentages relate to the total number in the group, and rounded to the nearest whole number.
[2] The numbers in the 'no analgesic cohort', given for comparison.
[3] 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, dipyrone ≥ 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 (%)[1]	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 (%)
AEs[2]								
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)[3]	138 (11)	158 (27)	16 (44)	312 (16)	55 (4)	16 (4)	1 (4)	72 (4)
Reasons for premature race withdrawal								
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)[4]	66 (5)	7 (1)	2 (5)	75 (4)	89 (6)	4 (1)	0 (0)	93 (5)
Pain post exercise								
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)

[1] Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

[2] 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

[3] Number of individuals reporting AEs (a single individual may report >1 AE)

[4] The difference of withdrawals comparing the analgesic and control cohort was not significant (p=0 237)

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[1] (%)	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)[2]	25 (4)	22 (10)	56 (14)	163 (52)	25 (25)	34 (87)	11 (10)	12 (18)

[1] % relative to the size of the group. Percentages rounded to the nearest whole number.

[2] 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

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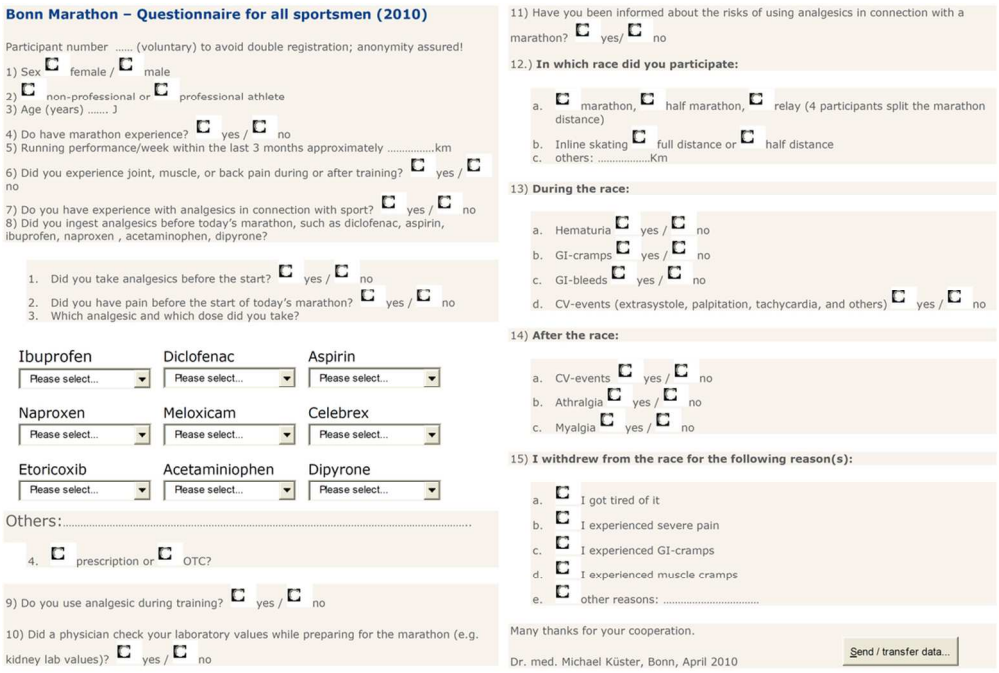


Bonn Marathon – Questionnaire for all sportsmen (2010)

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	Diclofenac	Aspirin
Please select...	Please select...	Please select...
Naproxen	Meloxicam	Celebrex
Please select...	Please select...	Please select...
Etoricoxib	Acetaminiophen	Dipyrone
Please select...	Please select...	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):**

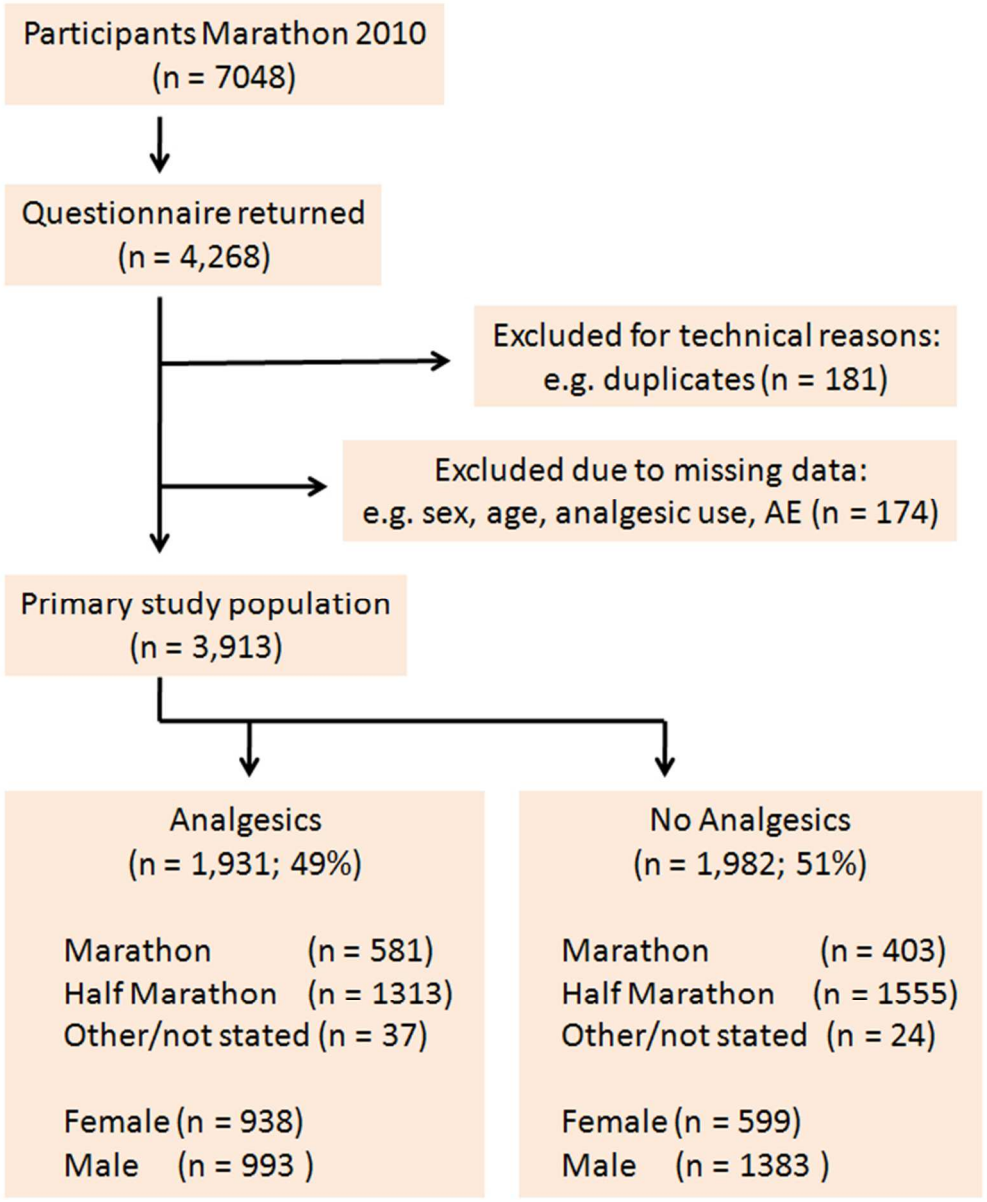
a. ☐ I got tired of it
b. ☐ I experienced severe pain
c. ☐ I experienced GI-cramps
d. ☐ I experienced muscle cramps
e. ☐ other reasons: .....

Many thanks for your cooperation.

Dr. med. Michael Küster, Bonn, April 2010

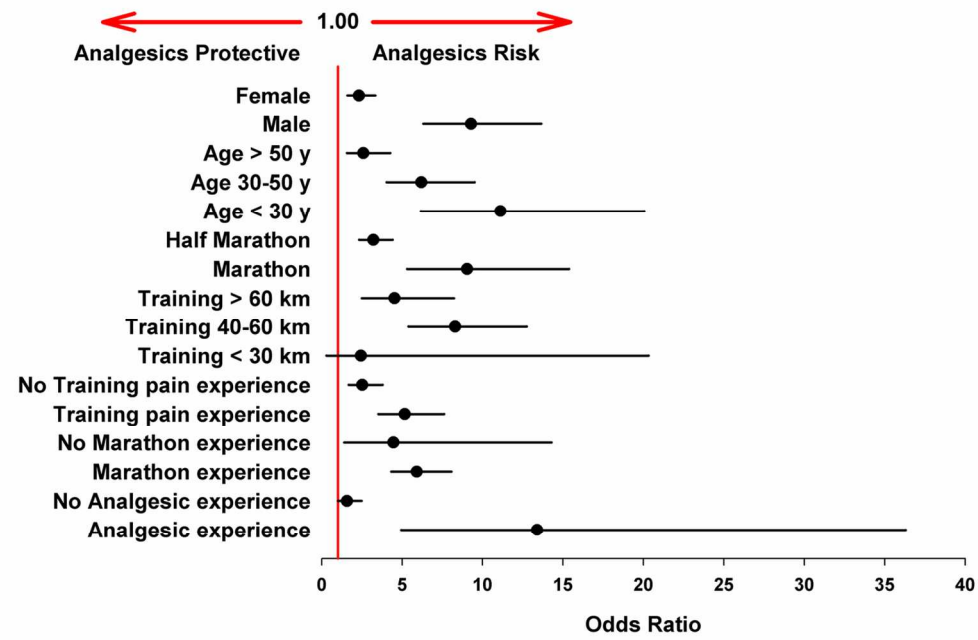
Send / transfer data...

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

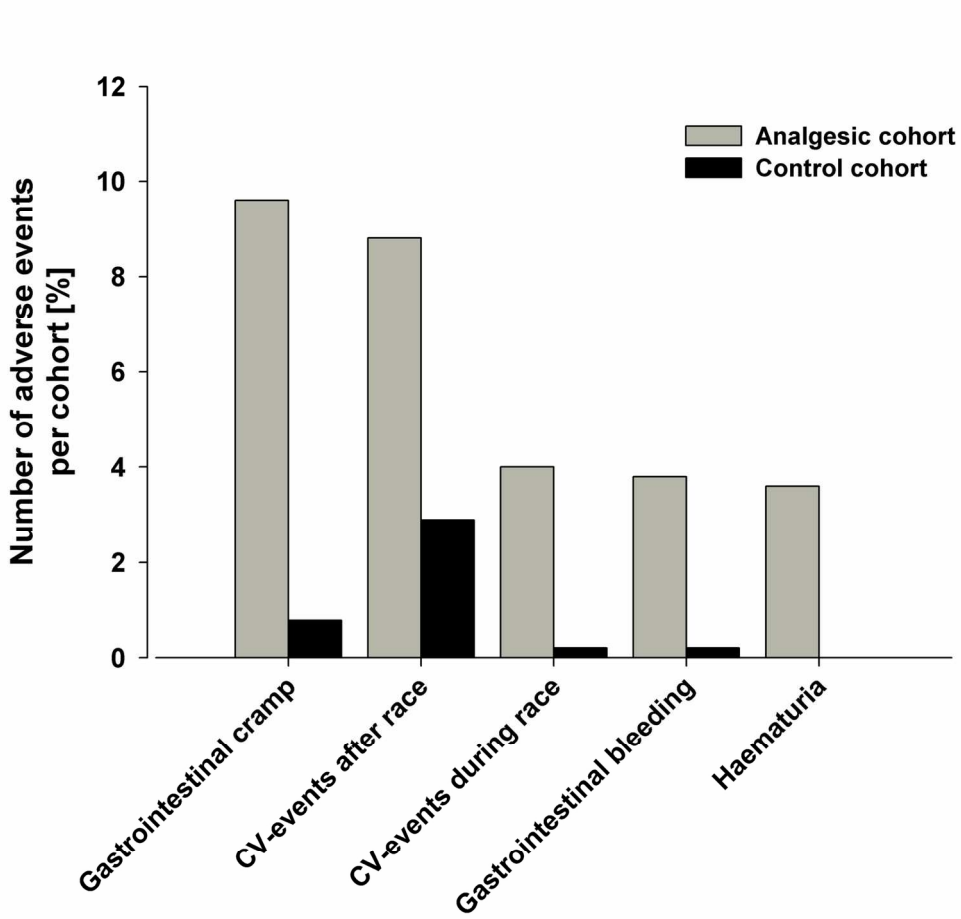


Flow chart of the evaluation of the marathon/half marathon running cohort.
After the elimination of duplicates, almost 2,000 questionnaires were returned from each cohort. The distribution of marathon and half-marathon runners was similar in each treatment cohort. If participants entered races other 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)

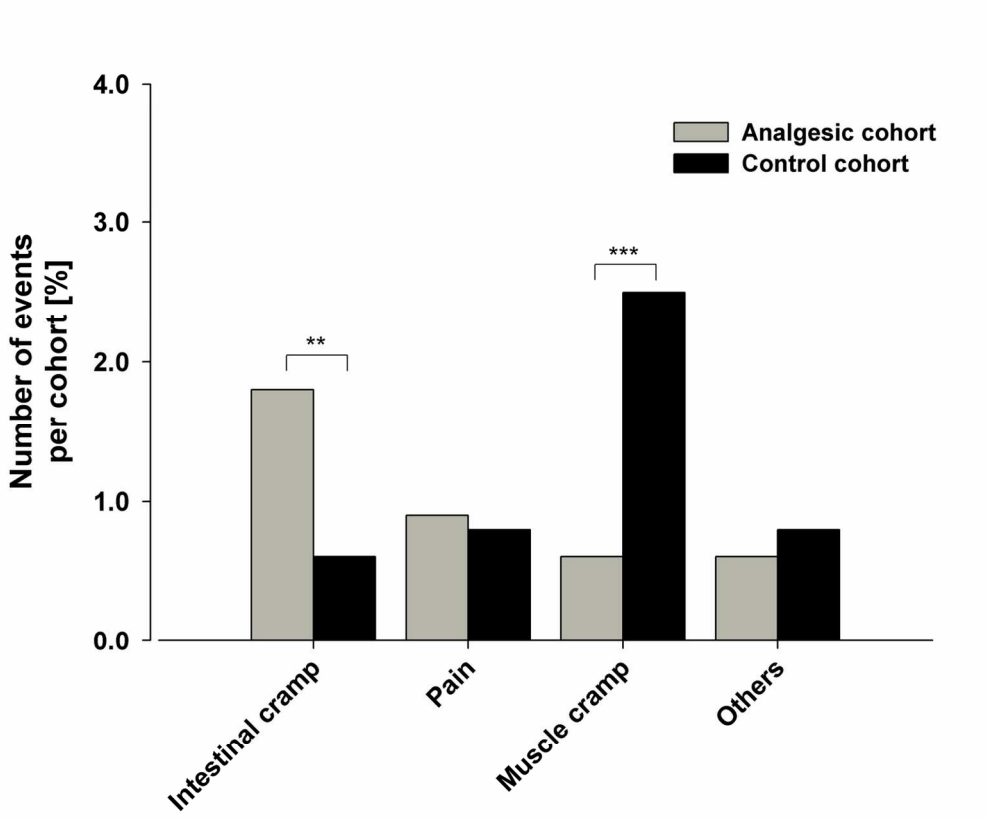


Risk of adverse events (AEs) within study subgroups (unadjusted). Odds ratios were estimated by binary linear regression analysis. Almost all subgroups show enhanced risk for AEs after analgesic use (odds ratios >1).
124x79mm (300 x 300 DPI)



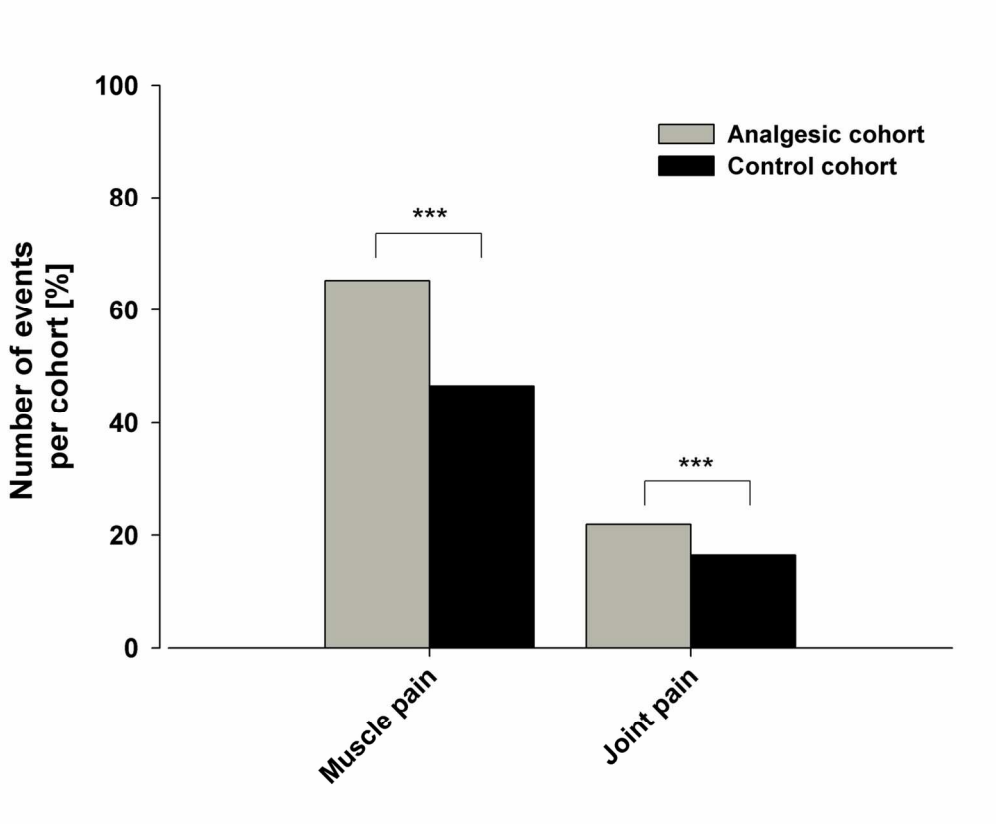
Incidence of adverse events (AEs, derived from Table 3)
Rounded percentages are given in Table 3
The differences between the groups were all highly significant; p<0•001.

150x144mm (300 x 300 DPI)



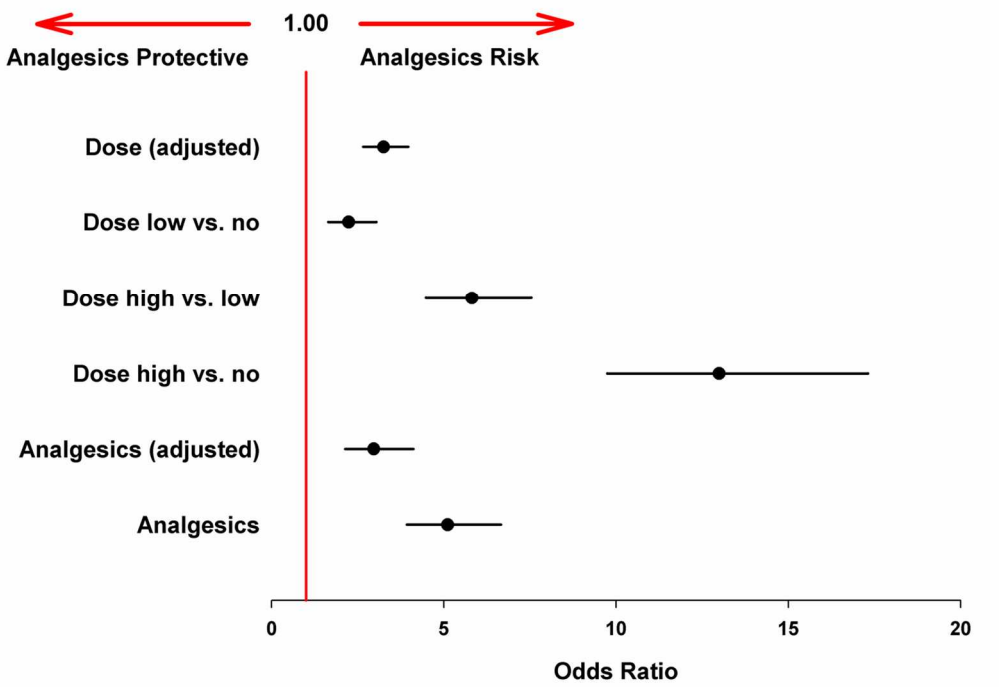
Reasons for premature termination of the race.
Rounded percentages are given in Table 3
**p<0•01
***p<0•001
Note: the absolute numbers are small.

137x117mm (300 x 300 DPI)



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)



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

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

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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

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

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 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[5]. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice[5]. 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.

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

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

Results

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

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

Background epidemiology

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

Medication use before racing

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

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

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

Events during and after the race:

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

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

A four to ten times higher incidence of each type of AE was observed in the analgesics cohort compared with controls (overall incidence 16% vs 4%. Table S3, Figure 3), with a calculated risk difference of 13%. The difference in the incidence of AEs between the two cohorts was most prominent with respect to GI cramps and CV-events (after race). In the analgesics cohort, GI cramps were the most frequent AE (reported by 14% of the cohort), followed by CV AEs after the race (9%). In the controls, CV AEs after the race were the most frequently reported AE (3%, Table S3). Notably, haematuria was reported only in the analgesics cohort. The differences in the incidence of all AEs were highly significant between the two groups ($p<0.001$, Table S3, Figure 3).

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

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

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

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

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

associated with relatively numerous GI or kidney bleeds, compared with the other analgesics.

Serious cases

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

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

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

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

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. 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 hypothesise that their use is likely to suspend the mucosa- and kidney-protective[3] effects of PGE_2/PGI_2, thus augmenting the damaging effect of diminished blood flow[21] and oxygen supply for the GI mucosa and kidney[22]. 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[23], and that repeated inhibition of the production of endothelium-produced PGI_2 during CV stress, e.g. intensive exercise, may accelerate atherosclerosis[1, 2, 24].

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 hospitalisation 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 ($p< 0{\cdot}001$), 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 ($p< 0{\cdot}001$) 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[25]. 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[26-28].

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[23, 29]. 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 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, 30-32].

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. Although the two cohorts were of similar sizes, there are differences between them with respect to age, sex, training, and drug experience (a contribution of long term use of OTC analgesic on the incidence of AEs cannot be excluded), which may also have influenced the outcome. However, the considerable homogeneity of the AEs seen throughout all subgroups supports the overall contention that cyclooxygenase inhibitors

taken before and during a marathon/half marathon race increase the risks of AEs substantially, without measurable benefit in terms of race completion.

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

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

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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[1] # 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)[2]	25 (4)	22 (10)	56 (14)	163 (52)	25 (25)	34 (87)	11 (10)	12 (18)

[1] % relative to the size of the group. Percentages rounded to the nearest whole number.

[2] Number of individuals reporting AEs (a single individual may report >1 AE)

See Table 2 for definition of dose sizes

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

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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

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

Abstract word count = 291

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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 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 ~~CV[11]~~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[5]. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice[5]. These results were confirmed by Gorski et al[18].

We now report a follow-up study aiming at defining the ~~of analgesic~~ use ~~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

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

A binary regression model was used to estimate odds ratios and 95% confidence intervals for AE incidence in subgroups and in the primary study population, with adjustment for confounding factors. Analyses were conducted using SPSS software version 19. Statistical tests were two-sided, and p-values less than 0.~~-~~05 were considered statistically significant. AEs from respondents who did not state which race they entered were not included in the marathon/half marathon sub-group analysis.

Results

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

The remaining 3,913 completed questionnaires constituted the primary study population, representing 56% of the participants in the Bonn marathon/half marathon 2010 (Figure ~~2~~1). Nearly half of the study cohort used analgesic before the actual race ('analgesic cohort': n=1931, 49%) and 51% reported not to have used any analgesic ('control group': n=1982; Figure 1).

Background epidemiology

Descriptive epidemiological data are given in Table S1 (supplementary information) ~~1~~. Overall, there were more men than women (2,376 vs. 1,537), and men were slightly older on average ~~(means: 38 and 43 years vs. 34 and 42 years).~~ (means ±SD: 40 ±10 vs. 39 ±11 years). Males and females were younger in the control group (means ±SD analgesic group: male 43 ±8, female 42 ±8 years vs. control group: male 38 ±12, female 34 ±13 years).

~~A larger proportion of men used analgesics during training.~~ Most respondents ~~(66-99%)~~ had previous marathon experience (overall 87%). In the ~~group who took analgesics before or during the marathon/half marathon (~~'analgesics cohort'~~)~~, ~~14-26%~~ 20% had also taken analgesics during training (male 26% vs. female 14%),

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

Medication use before racing

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

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

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

Events during and after the race:

The incidence of reported AEs was significantly higher in runners of the full marathon compared with the half-marathon (18% vs 7%; p<0~~.~~.001). Additionally, the analgesic related AE risk in the full marathon cohort was significantly higher than in the half marathon cohort (odds 9~~.~~.04; 95% CI 5~~.~~.31-15~~.~~.39 vs 3~~.~~.20; CI 2~~.~~.32-4~~.~~.42. Figure ~~3~~2).

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

A four to ten times higher incidence of each type of AE was observed in the analgesics cohort compared with controls (overall incidence 16%~~4%~~ vs 4% ~~16%~~. Table S3, Figure ~~4~~3), with a calculated risk difference of 13%. The difference in the

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

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

Joint and muscle pain after the race were significantly more frequent in the analgesics cohort than in controls (1,301 vs 955 respondents, p<0.001, Table S3, Figure ~~6~~5).

The overall risk for analgesic related AEs was estimated at 5.1 (95% CI 3.9-6.7; p<0.001, Figure ~~7~~6), giving a 'number needed to harm' of eight treated ~~people~~participants. In a subsequent subgroup analysis for sex, age, training, marathon/half marathon run, and analgesic experience, an enhanced risks (odds ratio) for the different subgroups was detected, but this was very variable (1.6-13.4, Figure ~~3~~2). Therefore, these subgroup parameters were included in a regression analysis which resulted in a comparable adjusted analgesic related risk of ~~3~~ 3.0 (95% CI ~~2~~ 2.1-~~4~~ 4.1; p<0.001, Figure ~~7~~6).

To investigate if the incidence of AEs was dose-dependent, a risk estimation of the size of the dose was conducted. The high dose resulted in a significantly higher risk 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~~6). This further adjusted regression model showed a statistically significant increased risk at rising doses, meaning that increasing the dose can increase the risk of AEs by three times (odds ratio 3.2; 95% CI, ~~2~~ 2.7-~~4~~ 4.0, p<0.001, Figure ~~7~~6).

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

Serious cases

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

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

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

infarctions. Both athletes recovered, although some cardiac damage remained in one respondent.

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

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. This investigation showed that most athletes taking analgesics had ~~either~~ taken ~~unsuitable drugs or~~ 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 ~~it~~ 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 hypothesise that their use is likely to suspend the mucosa- and kidney-protective[3] effects of PGE_2/PGI_2, thus augmenting the damaging effect of diminished blood flow[21] and oxygen supply for the GI mucosa and kidney[22]. 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[23], and that repeated inhibition of the production of endothelium-produced PGI_2 during CV stress, e.g. intensive exercise, may accelerate atherosclerosis[1, 2, 24].

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 hospitalisation 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 ($p< 0{\cdot}001$), 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 ($p< 0{\cdot}001$) 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[25]. 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 ~~a few~~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[26-28].

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[23, 29]. 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 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 ~~5, Table 4~~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, 30-32].

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. Although the two cohorts were of similar sizes, there are differences between them with respect to age, sex, training, and drug experience (a contribution of long term use of OTC analgesic on the incidence of AEs cannot be excluded), which may also have influenced the outcome. However, the considerable homogeneity of the AEs seen throughout all subgroups supports the overall contention that cyclooxygenase inhibitors taken before and during a marathon/half marathon race increase the risks of AEs substantially, without measurable benefit in terms of race completion.

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

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

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Table ~~4~~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[1] # 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)[2]	25 (4)	22 (10)	56 (14)	163 (52)	25 (25)	34 (87)	11 (10)	12 (18)

[1] % relative to the size of the group. Percentages rounded to the nearest whole number.

[2] Number of individuals reporting AEs (a single individual may report >1 AE)

See Table 2 for definition of dose sizes

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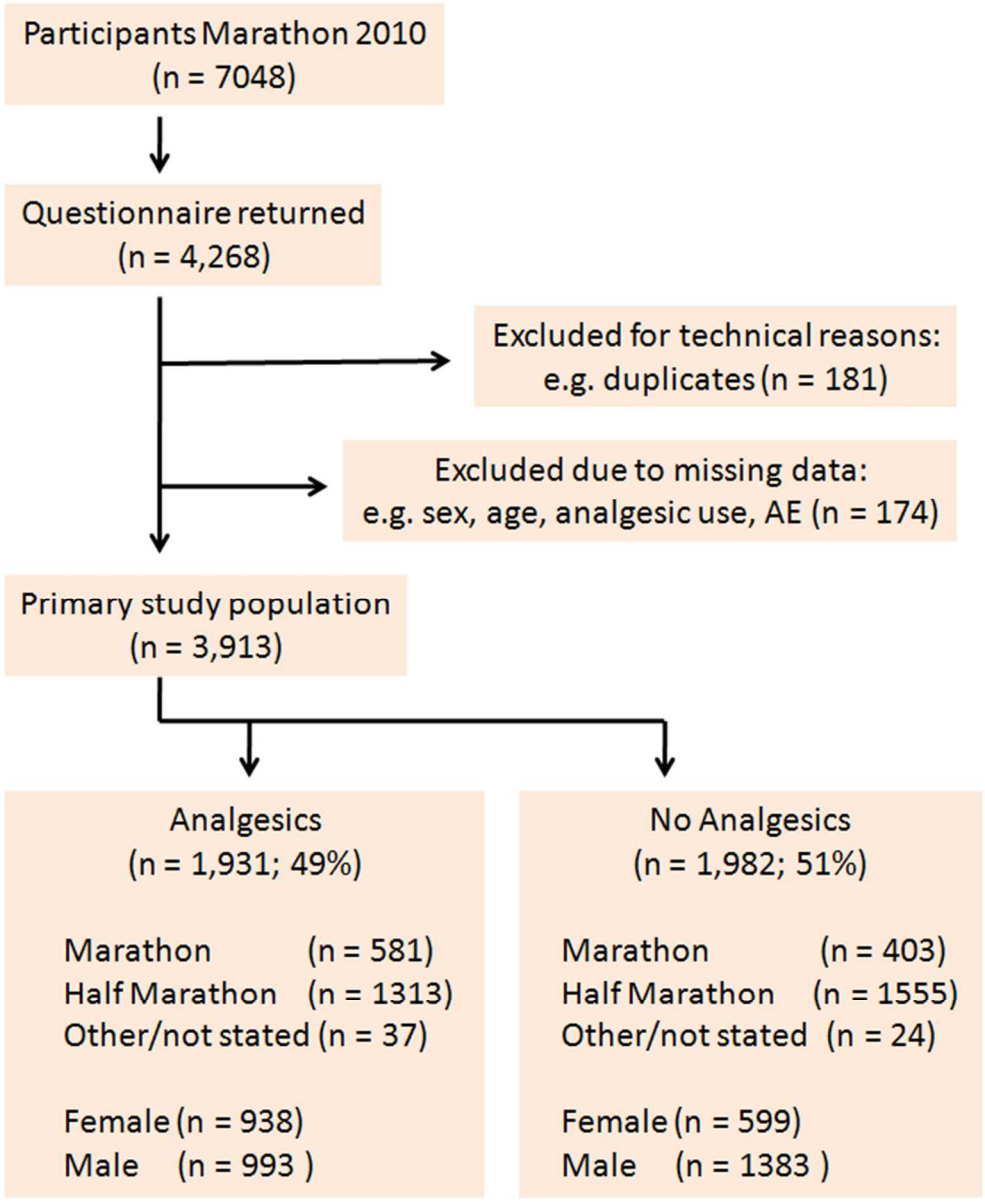


Figure 1: Flow chart of the evaluation of the marathon/half marathon running cohort.
After the elimination of duplicates, almost 2,000 questionnaires were returned from each cohort. The distribution of marathon and half-marathon runners was similar in each treatment cohort. If participants entered races 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)

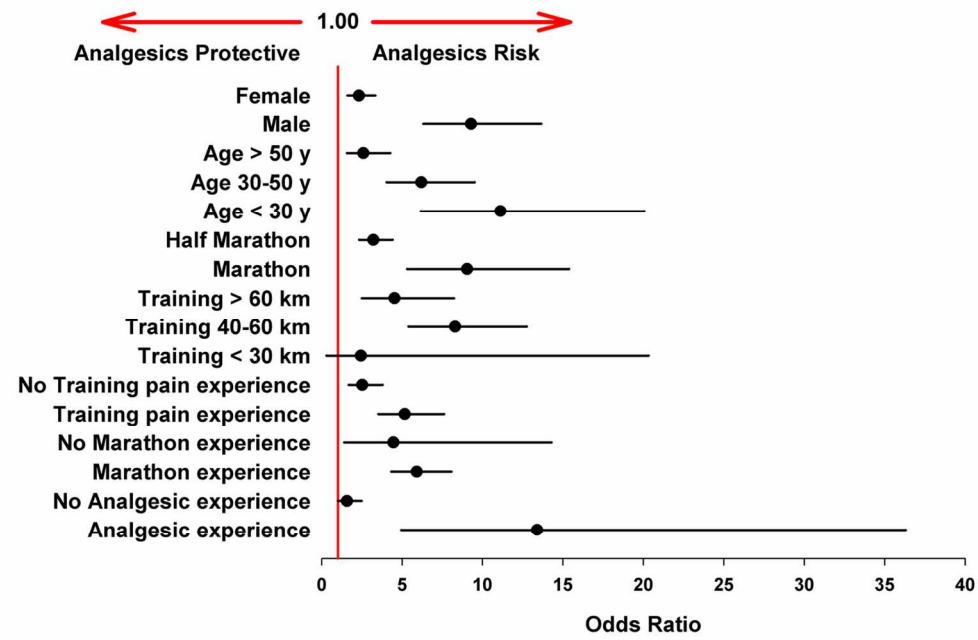


Figure 2: Risk of adverse events (AEs) within study subgroups (unadjusted). Odds ratios were estimated by binary linear regression analysis. Almost all subgroups show enhanced risk for AEs after analgesic use (odds ratios >1; error bars represent CI95%).
124x79mm (300 x 300 DPI)

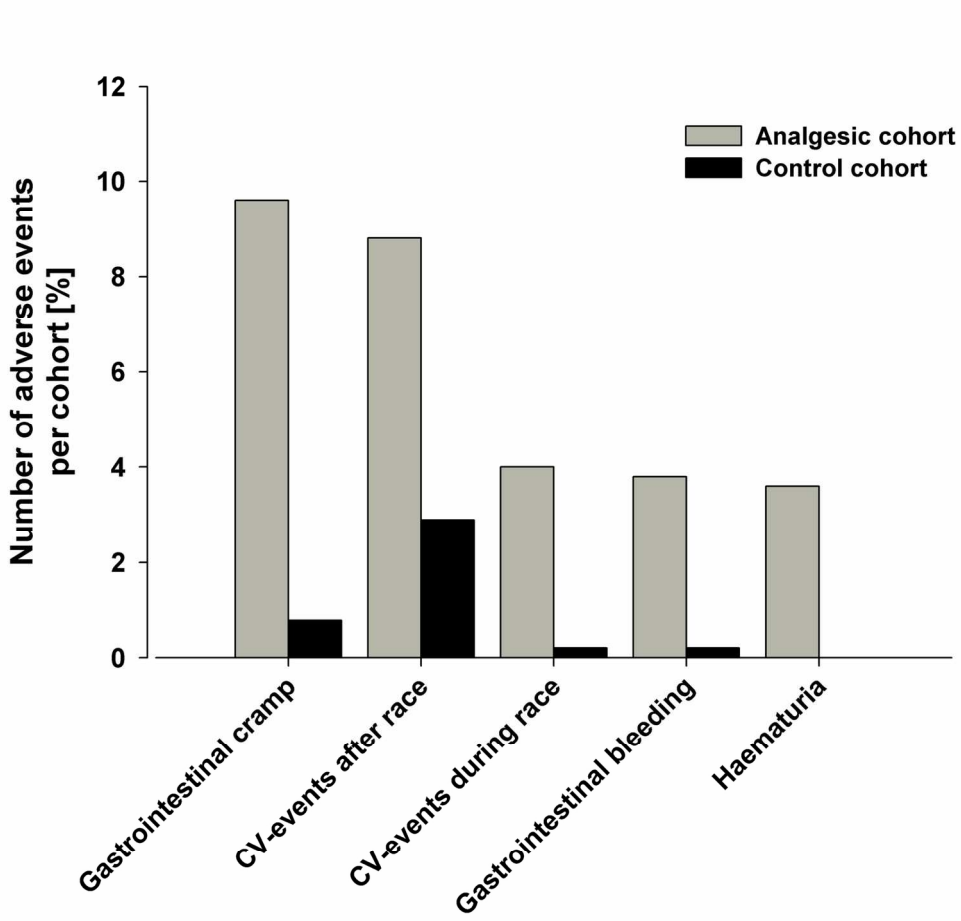


Figure 3: Incidence of adverse events (AEs, derived from Table S3)
Rounded percentages are given in Table S3
The differences between the groups were all highly significant; p<0.001.
150x144mm (300 x 300 DPI)

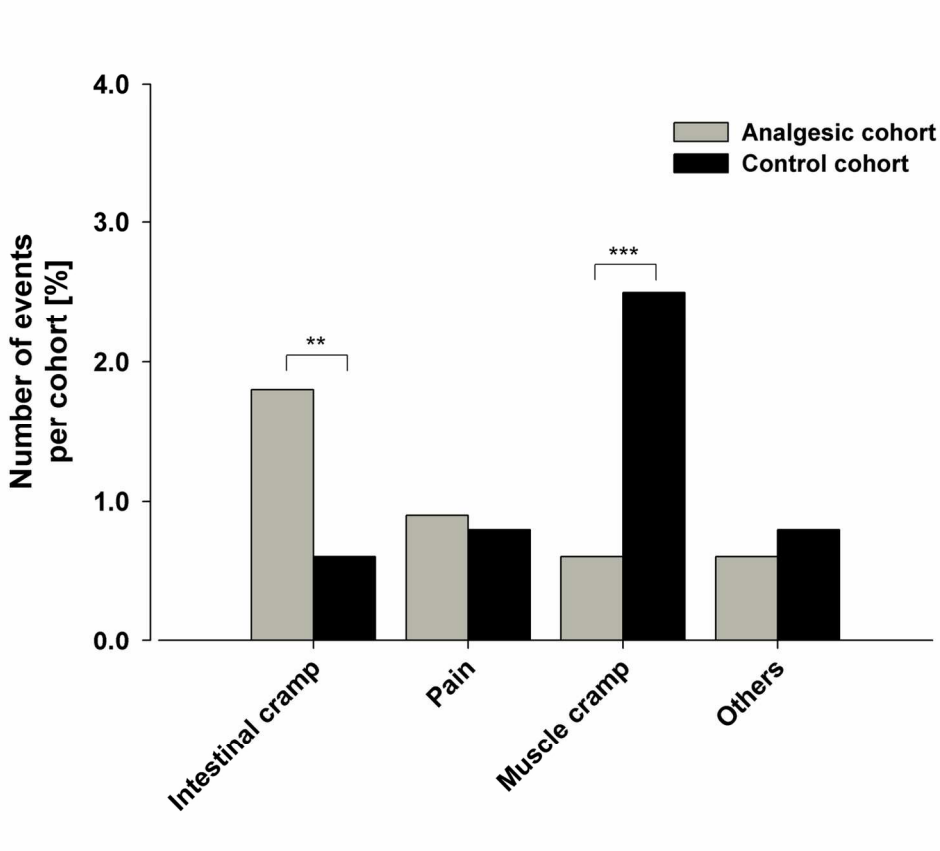


Figure 4: Reasons for premature termination of the race.
Rounded percentages are given in Table S3
**p<0.01
***p<0.001
Note: the absolute numbers are small.
137x117mm (300 x 300 DPI)

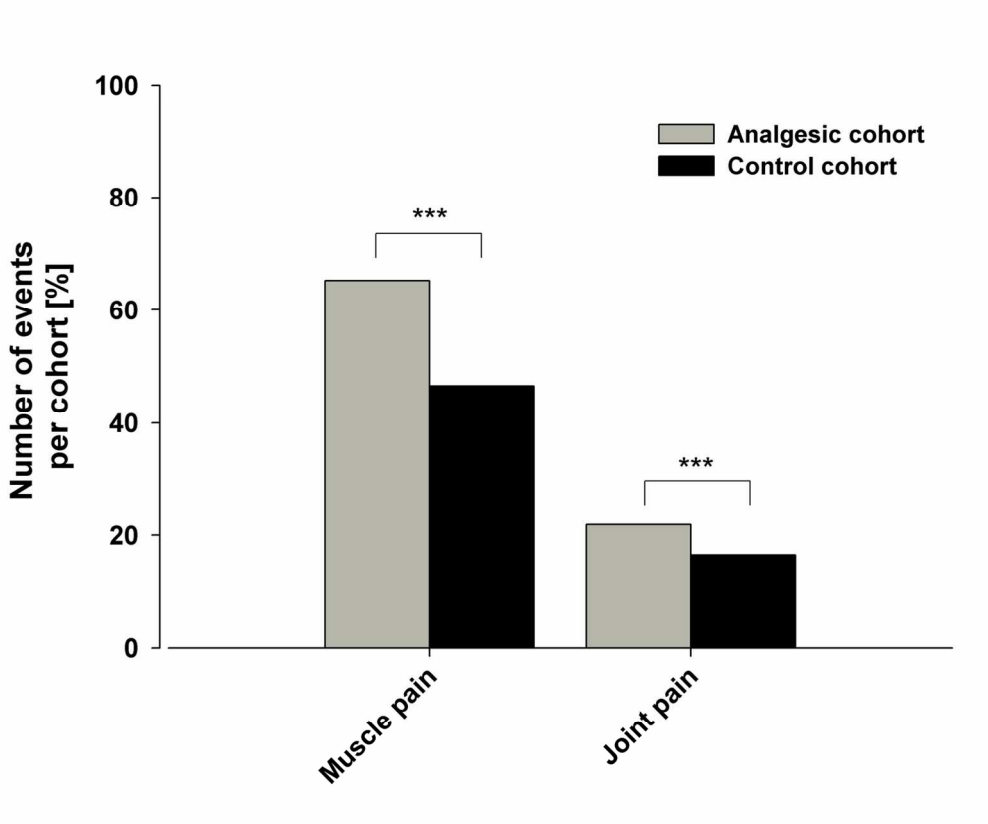


Figure 5: Percentage of runners experiencing muscle and/or joint pain after the race.
Rounded percentages are given in Table S3
The differences are highly significant (*** $p < 0.001$).
131x108mm (300 x 300 DPI)

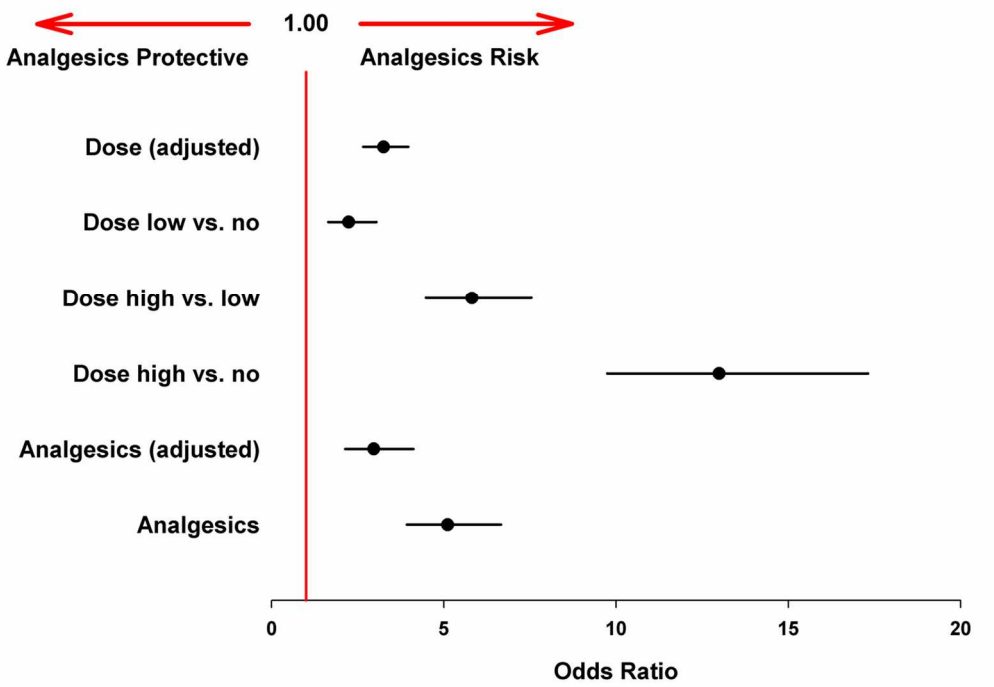
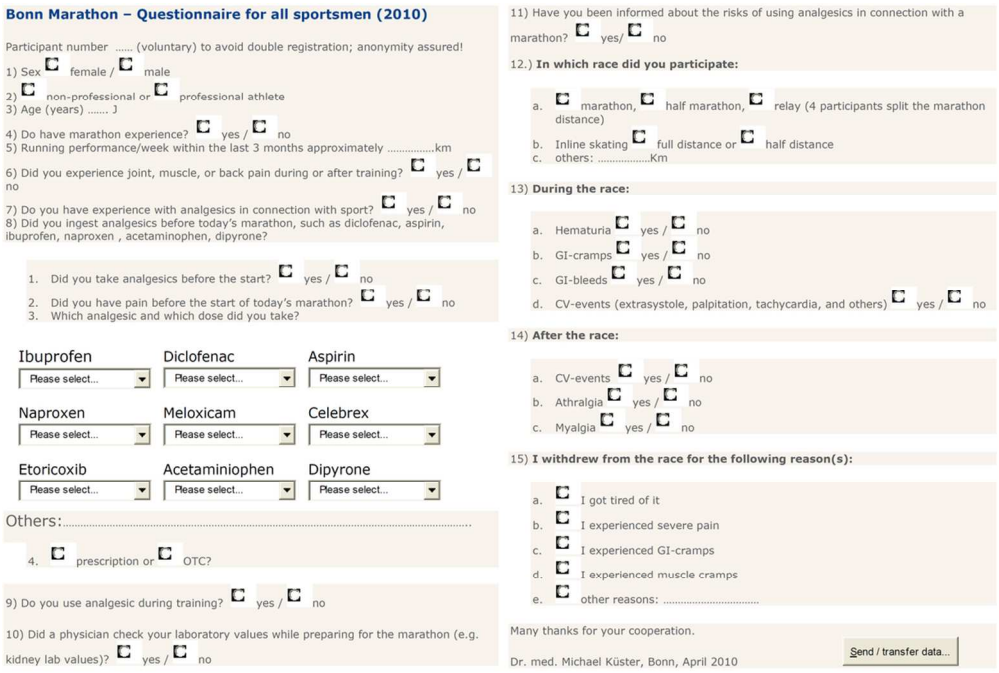


Figure 6: Adjusted adverse event (AE) risks for analgesic use and dose dependency
There was a significant dose/AE relationship and reported odds ratios increased with increasing dose differences (Dose no = controls without analgesic use). Adjusted odds ratios were estimated by binary linear regression 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	Diclofenac	Aspirin
Please select...	Please select...	Please select...
Naproxen	Meloxicam	Celebrex
Please select...	Please select...	Please select...
Etoricoxib	Acetaminiophen	Dipyrone
Please select...	Please select...	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 # of cases (%)[#]	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[1]	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).

[1] Lab check; Laboratory parameters tested before the race (e.g. kidney values; see question 10 in figure 1)

Table S2: Use of analgesics before the marathon

Drugs	Doses	All n=1,931 # of cases (%)[1]	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[2]	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[3]	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)

[1] Percentages relate to the total number in the group, and rounded to the nearest whole number.
[2] The numbers in the 'no analgesic cohort', given for comparison.
[3] 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, dipyrone ≥ 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 (%)[1]	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 (%)
AEs[2]								
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)[3]	138 (11)	158 (27)	16 (44)	312 (16)	55 (4)	16 (4)	1 (4)	72 (4)
Reasons for premature race withdrawal								
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)[4]	66 (5)	7 (1)	2 (5)	75 (4)	89 (6)	4 (1)	0 (0)	93 (5)
Pain post exercise								
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)

[1] Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

[2] 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

[3] Number of individuals reporting AEs (a single individual may report >1 AE)

[4] 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	Haemofiltra-tion, electrolytes, furosemide for 10 days	Incompletely recovered
4	Aspirin (500 mg BS)	Dysmen-orrhoea	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 perfor-mance	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 infarc-tion	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
Title and abstract	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
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
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
Results		
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
Discussion		
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
Other information		
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

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

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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[5]. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice[5]. 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

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

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

Results

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

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

Background epidemiology

Descriptive epidemiological data are given in Table S1 (supplementary information). Overall, there were more men than women (2,376 vs. 1,537), and men were slightly older on average (means ±SD: 40 ±10 vs. 39 ±11 years). Males and females were younger in the control group (means ±SD analgesic group: male 43 ±8, female 42 ±8 years vs. control group: male 38 ±12, female 34 ±13 years). Most respondents had previous marathon experience (overall 87%). In the analgesics cohort, 20% had also taken analgesics during training (male 26% vs. female 14%), compared with 1% of the control group. Of the analgesics cohort, 11% recorded pain before the race

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

Medication use before racing

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

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

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

Events during and after the race:

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

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

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

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

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

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

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

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

Finally, the association of analgesic use with distinct side effect profiles was analysed. The ingestion of all three drugs used most frequently (aspirin, diclofenac, and ibuprofen) was associated with AEs in a dose-dependent manner (Table 1). Overall, the "drug related" incidence (defined as the percentage of respondents

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

Serious cases

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

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

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

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

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_2/PGI_2, 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_2 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 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,

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

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

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

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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 (%)[1]	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)[2]	25	22	56	163	25	34	11	12
Drug related AE incidence	4%	10%	14%	52%	25%	34%	11%	12%

[1] Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.
[2] 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.

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

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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[5]. We found that over half of the participating athletes ingested analgesics before racing, most of them without medical advice[5]. 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

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

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

Results

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

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

Background epidemiology

Descriptive epidemiological data are given in Table S1 (supplementary information). Overall, there were more men than women (2,376 vs. 1,537), and men were slightly older on average (means ±SD: 40 ±10 vs. 39 ±11 years). Males and females were younger in the control group (means ±SD analgesic group: male 43 ±8, female 42 ±8 years vs. control group: male 38 ±12, female 34 ±13 years). Most respondents had previous marathon experience (overall 87%). In the analgesics cohort, 20% had also taken analgesics during training (male 26% vs. female 14%), compared with 1% of the control group. Of the analgesics cohort, 11% recorded pain before the race

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

Medication use before racing

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

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

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

Events during and after the race:

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

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

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

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

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

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

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

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

Finally, the association of analgesic use with distinct side effect profiles was analysed. The ingestion of all three drugs used most frequently (aspirin, diclofenac, and ibuprofen) was associated with AEs in a dose-dependent manner (Table 1). Overall, the "drug related" incidence (defined as the percentage of respondents

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

Serious cases

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

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

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

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

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_2/PGI_2, 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_2 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~~hospitalisation~~ 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,

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

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

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

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

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 reportse ases (%)[1]	High dose n=220 no.# of reportse ases (%)	Low dose n=410 no.# of reportse ases (%)	High dose n=312 no.# of reportse ases (%)	Low dose n=102 no.# of reportse ases (%)	High dose n=39 no.# of reportse ases (%)	Low dose n=107 no.# of reportse ases (%)	High dose n=68 no.# of reportse ases (%)
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)[2]	25	22	56	163	25	34	11	12
Drug related AE incidence	4%	10%	14%	52%	25%	34%	11%	12%

[1] 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.

[2] Number of individuals reporting AEs (a single individual may report >1 AE)

See Table S2 for definition of dose sizes

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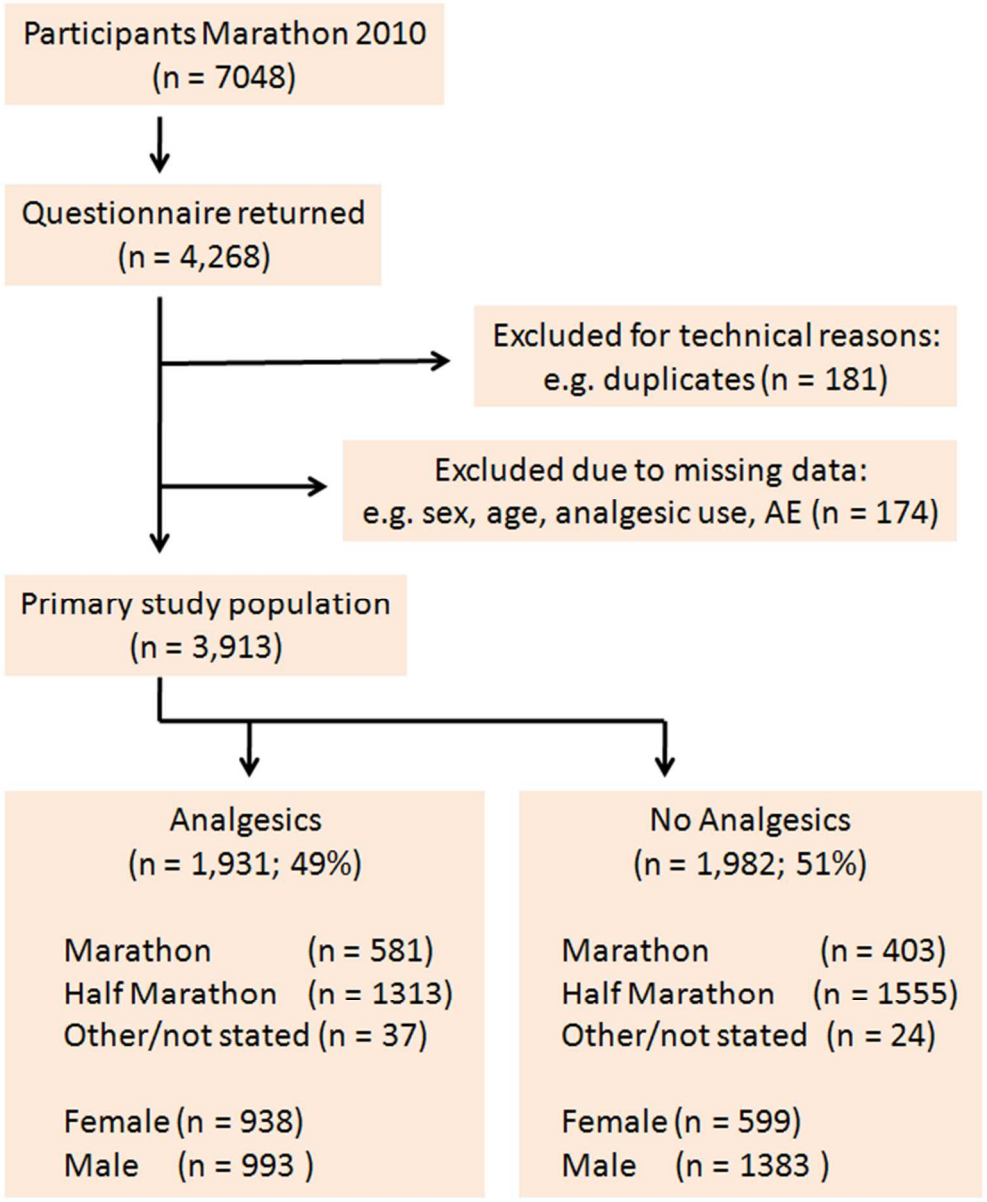


Figure 1: Flow chart of the evaluation of the marathon/half marathon running cohort.
After the elimination of duplicates, almost 2,000 questionnaires were returned from each cohort. The distribution of marathon and half-marathon runners was similar in each treatment cohort. If participants entered races 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)

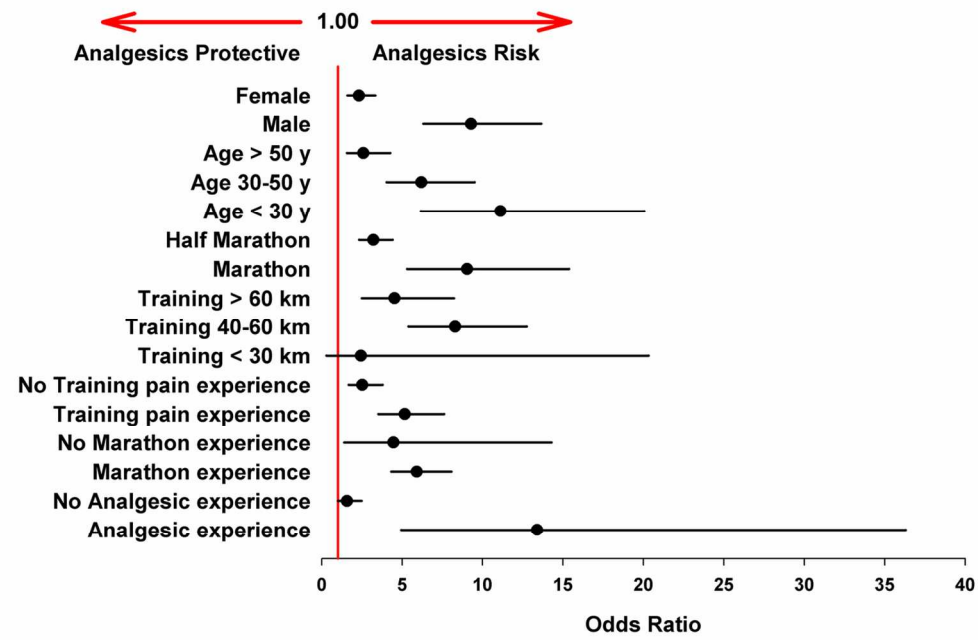


Figure 2: Risk of adverse events (AEs) within study subgroups (unadjusted). Odds ratios were estimated by binary linear regression analysis. Almost all subgroups show enhanced risk for AEs after analgesic use (odds ratios >1; error bars represent CI95%).
124x79mm (300 x 300 DPI)

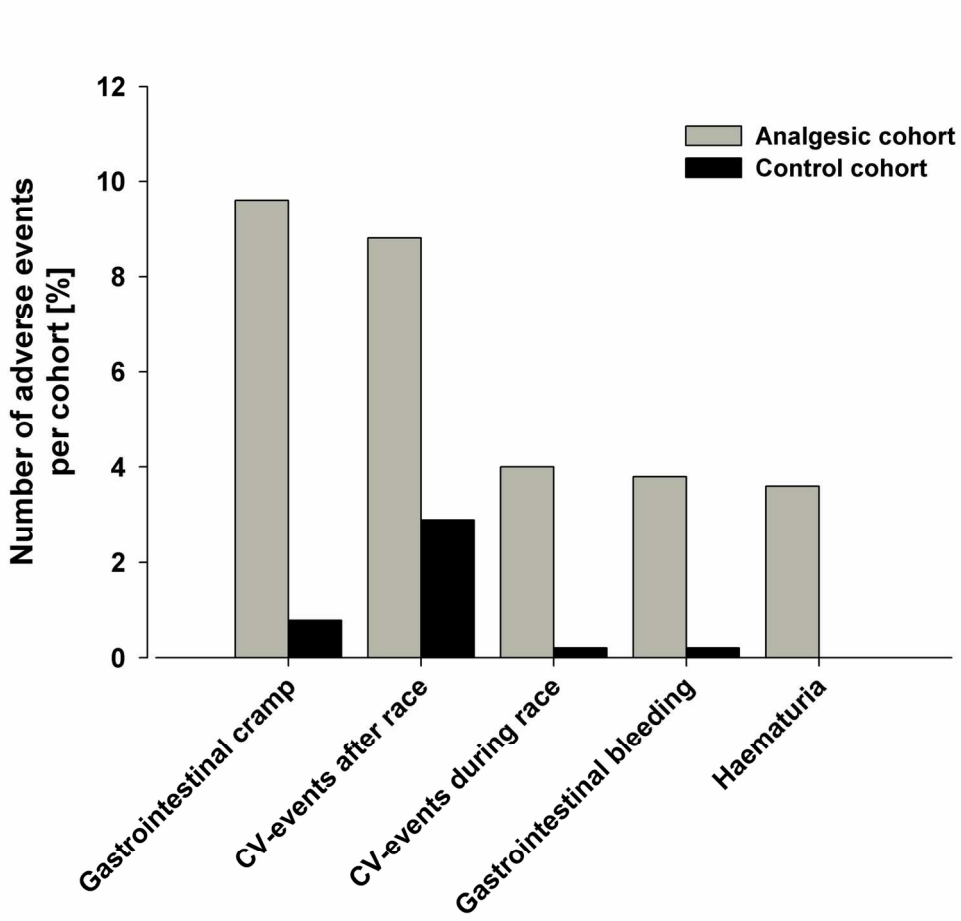


Figure 3: Incidence of adverse events (AEs, derived from Table S3)
Rounded percentages are given in Table S3
The differences between the groups were all highly significant; p<0.001.
150x144mm (300 x 300 DPI)

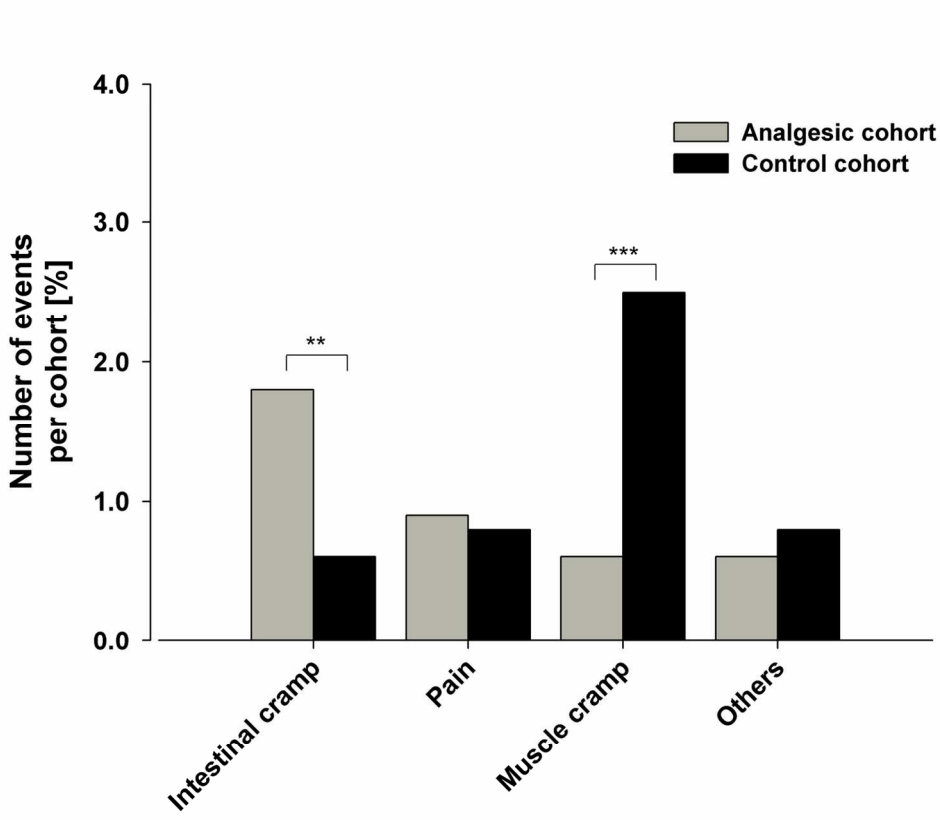


Figure 4: Reasons for premature termination of the race.
Rounded percentages are given in Table S3
**p<0.01
***p<0.001
Note: the absolute numbers are small.
137x117mm (300 x 300 DPI)

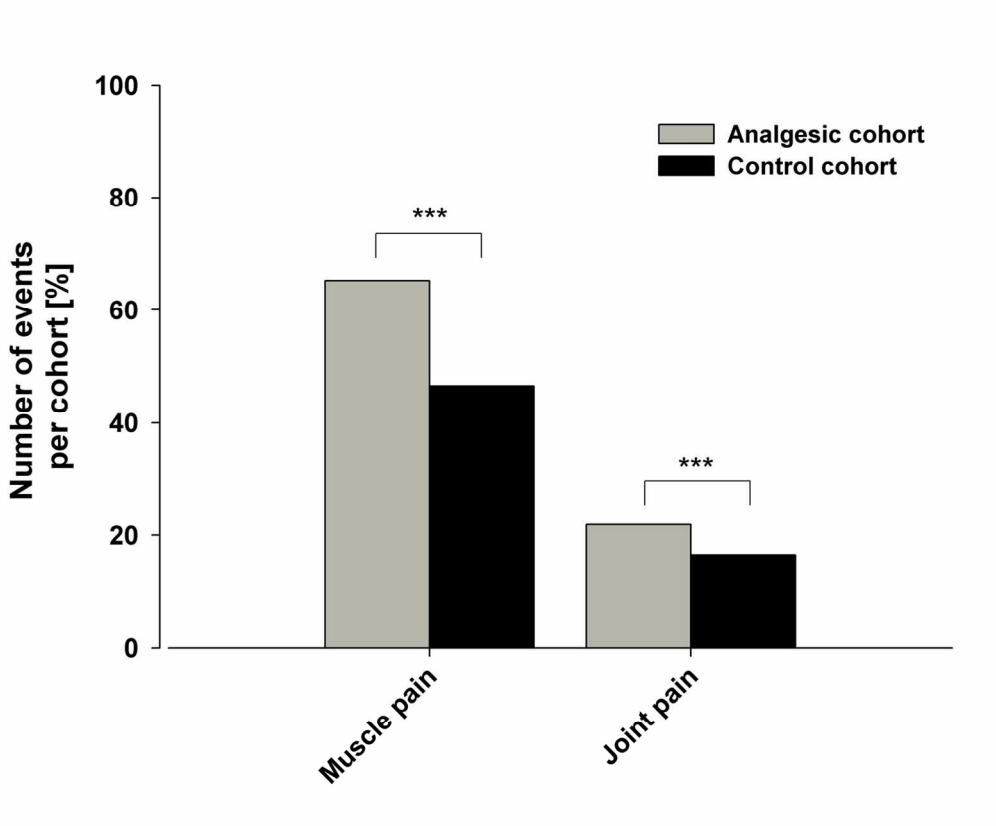


Figure 5: Percentage of runners experiencing muscle and/or joint pain after the race.
Rounded percentages are given in Table S3
The differences are highly significant (*** $p < 0.001$).
131x108mm (300 x 300 DPI)

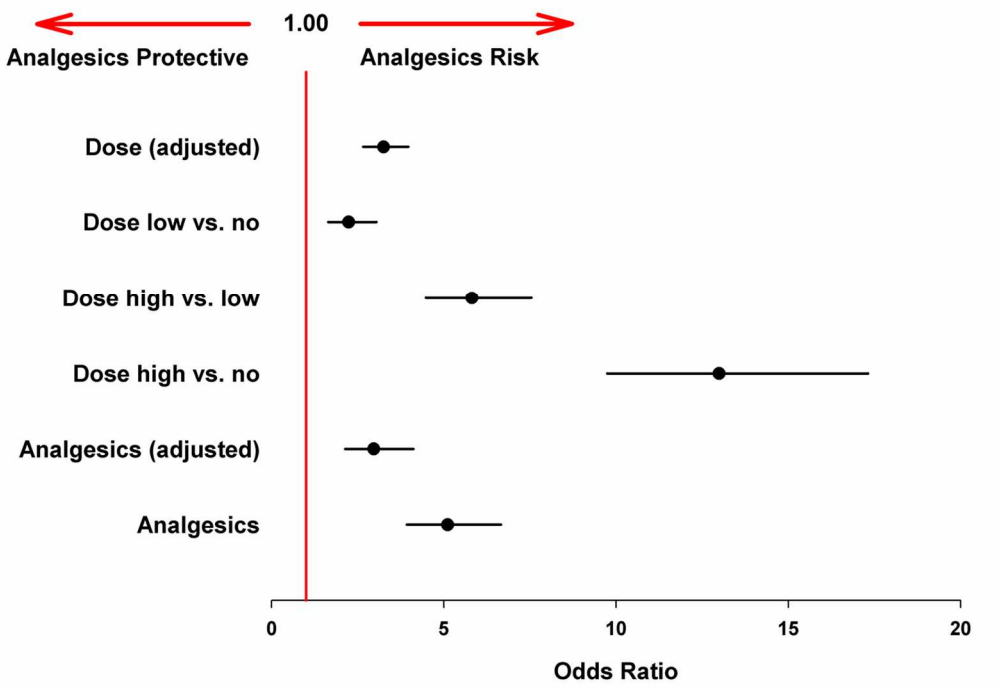
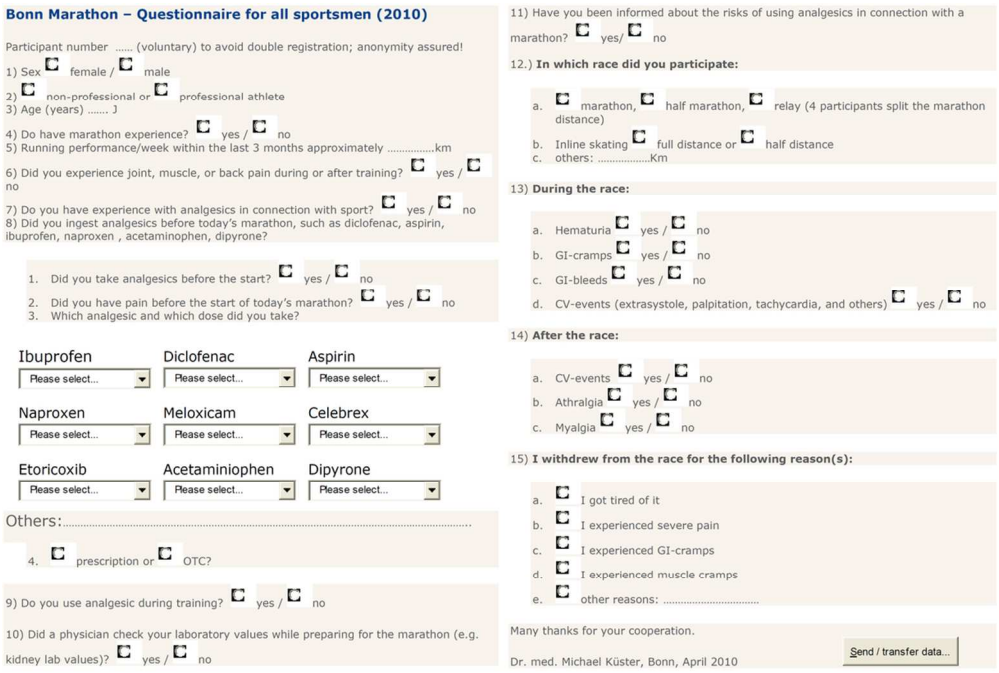


Figure 6: Adjusted adverse event (AE) risks for analgesic use and dose dependency
There was a significant dose/AE relationship and reported odds ratios increased with increasing dose differences (Dose no = controls without analgesic use). Adjusted odds ratios were estimated by binary linear regression 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	Diclofenac	Aspirin
Please select...	Please select...	Please select...
Naproxen	Meloxicam	Celebrex
Please select...	Please select...	Please select...
Etoricoxib	Acetaminiophen	Dipyrone
Please select...	Please select...	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 no. of cases (%)[#]	Male n=993 no. of cases (%)	All** Female and Male n=1931 no. of cases (%)	Female n=599 no. of cases (%)	Male n=1,383 no. of cases (%)	All** Female and Male n=1,982 no. of cases (%)	Total n=3,913 # 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[1]	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).

[1] 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 (%)[1]	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[2]	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[3]	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)

[1] Percentages: number of reports relate to the total number in the group, and rounded to the nearest whole number.

[2] Number of individuals reporting "None" in the 'analgesic cohort', given for comparison.

[3] 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, dipyrone ≥ 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 no. of reports (%)[1]	Marathon n=581 no. of reports (%)	Other /not stated n=37 no. of reports (%)	All n=1,931 no. of reports (%)	Half marathon n=1,555 no. of reports (%)	Marathon n=403 no. of reports (%)	Other /not stated n=24 no. of reports (%)	All n=1,982 no. of reports (%)
AEs[2]								
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)[3]	138	158	16	312	55	16	1	72
Reasons for premature race withdrawal								
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)[4]	66	7	2	75	89	4	0	93
Pain post exercise								
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

[1] Percentages relate to the corresponding subpopulations, and rounded to the nearest whole number.

[2] 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

[3] Number of individuals reporting AEs (a single individual may report >1 AE)

[4] 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
Title and abstract	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
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
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
Results		
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
Discussion		
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
Other information		
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.