Evaluation of nonsteroidal anti-inflammatory drugs and caffeine consumption in the Gran Trail Aneto Posets races

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Summary

Introduction: To know and analyze the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) and caffeine globally and specifically in each of the six mountain races (MR) of the Gran Trail Trangoworld Aneto Posets (GTTAP).
Material and method: A descriptive cross-sectional study carried out at the10th edition of the GTTAP held in Benasque, July 20-23, 2023. All participants in any of these races were invited to anonymously and voluntarily complete a questionnaire with a series of questions mainly referring to the use of NSAIDs and caffeine in the GTTAP races. The variables of interest were age (grouped into 7 different ranges), gender, number of participants in each of the GTTAP races, athletes who completed or dropped out, use of NSAIDs, caffeine, or a combination of both drugs, and symptoms they presented.
Results: A total 2,965 athletes participated, and 751 surveys were received (25.3%). 575 (76.6%) were men, and 176 (23.4%) were women. The average age was 41.74±10.1 years, average weight 69.03±10.99 kg, and average height 173.37±8.45 cm. Men's average age, weight and height were higher than women's. 258 athletes (34.4%) consumed NSAIDs; 15.5% only consumed NSAIDs, and 18.9% consumed NSAIDs and caffeine. 510 athletes (67.9%) consumed caffeine; 49% consumed it alone. Caffeine consumption was significantly higher than NSAIDs consumption (67.9% *vs* 34.4%).
Conclusions: NSAIDs and caffeine, being easily accessible drugs, are widely consumed in MR. Ibuprofen is the most consumed NSAID, and caffeine consumption exceeded NSAID consumption. Information and prevention campaigns are needed to address the risks of abusive consumption of these drugs.

Key words:
Mountain races. Nonsteroidal anti-inflammatory drugs. Ibuprofen. Caffeine. Consumption. Rhabdomyolysis.

Evaluación del consumo de antiinflamatorios no esteroideos y cafeína en las carreras que componen la Gran Trail Aneto Posets

Resumen

Introducción: El objetivo es conocer y analizar el consumo de antiinflamatorios no esteroideos (AINE) y cafeína de forma global y específica en cada una de las seis carreras de montaña (CM) de la Gran Trail Trangoworld Aneto Posets (GTTAP).
Material y método: Estudio descriptivo de corte transversal que se realizó en la 10ª edición de la GTTAP celebrada en Benasque, los días 20-23 de Julio de 2023. A todas las inscripciones en cualquiera de estas carreras, se les invitó a rellenar, de forma anónima y voluntaria, un cuestionario con una serie de preguntas principalmente referentes al consumo de AINE y cafeína en las carreras de la GTTAP. Las variables de interés fueron la edad (agrupados en 7 rangos diferentes), género, número de participantes en cada una de las carreras de la GTTAP, deportistas que finalizaron o, abandonaron, consumo de AINE, de cafeína o combinado de ambos fármacos y síntomas que presentaron.
Resultados: Participaron un total de 2.965 deportistas y se recibieron 751 encuestas (25,3%). El 575 (76,6 %) eran hombres y 176 (23,4%) mujeres. La edad media fue de 41,74±10,1 años, el peso medio 69,03±10,99 kilos y la talla 173,37± 8,45. La edad media de los hombres fue superior al de las mujeres, lo mismo que el peso y la talla. Consumieron AINE 258 (34,4%) deportistas, el 15,5% solo AINES, y el 18,9% AINE más cafeína. Consumieron cafeína 510 (67,9%) deportistas, el 49% la consumieron sola. El consumo de cafeína fue muy superior al de los AINE (67,9% *vs* 34,4%).
Conclusiones: Los AINE y la cafeína al ser fármacos de fácil adquisición su consumo está muy extendido en las CM. El ibuprofeno es el AINE más consumido y la cafeína ha tenido un consumo superior al AINE. Se necesita establecer campañas de información y prevención sobre el riesgo del consumo abusivo de estos fármacos.

Palabras clave:
Carreras de montaña. Antiinflamatorios no esteroideos. Ibuprofeno. Cafeína. Consumo. Rabdomiólisis.

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Introduction

Trail races (TR), especially long-distance races known as ultratrails, are extremely demanding and can even have negative health consequences for the participants[1]. These events combine challenging conditions, including changing weather, average altitudes above 2,000 m, constant terrain changes, and significant elevation gain over ascents and descents[2]. The characteristics of these races have been associated with a negative energy balance, muscle damage, inflammation, neuromuscular fatigue, cardiac dysfunction, myocardial injury with rhabdomyolysis, dehydration, and acute kidney failure[1-5]. This type of race, which requires extremely exhausting and prolonged exercise, is gaining popularity, and the available spots for registration often fill up quickly[6,7], as is the case with the TR of the Gran Trail Trangoworld Aneto Posets (GTTAP)/ Great Trangoworld Aneto-Posets Trail.

The sustained physical demand at a high level during these events induces a wide range of metabolic changes, causes microtears in the muscles and other tissues, which in turn increases the migration of white blood cells to the injury sites and triggers acute inflammatory reactions[8]. Moreover, TR involve significant amounts of eccentric muscle contractions, which can lead to exercise-induced pain and muscle damage, manifesting as elevated serum levels of myoglobin and creatine kinase (CK)[3,9]. The continuous foot strikes during the race require concentric and eccentric actions of the leg muscles, which may be responsible for muscle fiber injuries[10].

The medical care for the GTTAP is provided by more than 60 volunteer professionals from various fields, including medicine, nursing, physiotherapy, and podiatry. They are distributed across eleven medical points along the routes of the different races that make up the event, in addition to on-course doctors and a hospitalization area located at the Benasque Pavilion. Since the first editions, what stood out was not the muscle pain (which is fully justified)[3,8-10], but the significant number of athletes with vomiting, diarrhea, gastrointestinal pain, and dehydration who required urgent rehydration and electrolyte replenishment intravenously.

It is known that acute gastrointestinal (GI) problems are common during training and TR. Between 50 and 80% of athletes experience nausea, vomiting, or diarrhea[11-13]. Prolonged running has been shown to cause damage to the small intestine and increase intestinal permeability[14]. However, these symptoms generally resolve with the cessation of exercise and do not appear to cause long-term health problems. In extreme cases, though, they can lead to severe dehydration[7].

During exercise, renal blood flow is reduced as cardiac output is redirected to the muscles, resulting in a decrease in kidney function[15]. During TR, severe reductions in kidney function and kidney failure are very rare[16-19]. However, the risk of kidney injury can be exacerbated by factors such as endurance running in extreme environments (e.g., warm, cold, humid conditions, altitude, etc.), severe muscle damage with rhabdomyolysis due to high biomechanical loads, low fluid intake, GI pathology leading to dehydration, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and genetic predisposition[7,16-22].

The anamnesis of severe dehydration revealed significant NSAID use, even in the pre-race phase, alongside the consumption of caffeine gels or other products containing this substance. When dehydration[11-13], exercise-induced rhabdomyolysis[3,8-9], NSAID nephrotoxicity[18-22], and the risk associated with high caffeine consumption are combined, kidney function and even life can be compromised[23-26].

The main aim of the study was to assess the global and specific consumption of NSAIDs and caffeine in each of the TR of the GTTAP, with the goal of establishing information and prevention campaigns regarding the risks of excessive use of these drugs. The secondary objective was to identify the predominant symptoms experienced by the participants.

Material and method

Design and setting

A descriptive retrospective cross-sectional study was conducted during the 10th edition of the GTTAP (Benasque, July 20-23, 2023). The GTTAP includes six different TR:

- Gran Trail Aneto-Posets/ Great Trail Aneto-Posets: 105 km, elevation gain 6,760 m+.
- Vuelta al Aneto/ Return to Aneto: 55 km, elevation gain 3,630 m+.
- Maratón de las Tucas/ Marathon of the Tucas: 42 km, elevation gain 2,500 m+.
- Vuelta al Pico Cerler/ Back to Cerler: 26.9 km, elevation gain 1,250 m+.
- Vuelta al Molino de Cerler/ Tour of the Cerler Mill: 10.8 km, elevation gain 460 m+.
- Kilómetro Vertical (KV)/ KV Aneto-Posets: 5.4 km, elevation gain 980 m+.

Participants and data gathering

All registered athletes for any of these races were invited to anonymously and voluntarily complete a questionnaire that included a series of questions, such as: which race they were participating in, gender, age, height, weight, whether they completed the entire race or withdrew (and the reason for withdrawal), race time or time until withdrawal, reason for withdrawal (trauma, fatigue, nausea, vomiting, diarrhea, heat, etc.), whether they consumed any NSAIDs during the race, when they consumed the NSAID (before, during, or after), and which NSAID they used (options included ibuprofen, diclofenac, dexketoprofen, coxibs like etoricoxib, celecoxib, and others with specifications). They were also asked about the dose in milligrams (mg), name, and dose taken before, during, and after the race. Additionally, the questionnaire asked about the consumption of caffeine gels, pills, or gummies (number and mg or grams of caffeine consumed before and during the race), and whether they experienced any symptoms during the race, such as trauma pain, muscle pain, muscle cramps, nausea, vomiting, diarrhea, dizziness, palpitations, or others with specifications.

The questionnaire was validated before the GTTAP in training groups and during the Tozal de Guara half and full marathon (June 2023). Firstly, the questionnaire was answered anonymously and voluntary by mountain race training groups. A total of 64 runners answered the questionnaire. The purpose was to check the questionnaire's comprehension and collect feedback that could be used to improve it. The new

questionnaire was developed and validated during Tozal de Guara half and full marathons. The procedure was similar to that followed with the training groups. A total of 186 runners answered. They found the survey understandable and accurate, and it was the one used in the GTTAP.

The questionnaire was disseminated by sending an email to all registered participants, including a link to access the survey. This email was resent the day after the event. A QR code linking to the questionnaire was included in participants' race bags and displayed on posters at major participant medical points.

The research was conducted through an anonymous survey voluntarily signed by runners who wished to participate. Since the survey was both anonymous and voluntary, participants' rights to privacy and anonymity were safeguarded.

Since this questionnaire is anonymous and contains no sensitive personal information, poses no risk to participants, is not targeted at vulnerable populations, and provides sufficient and understandable information about the purpose of the research, explicit approval from the Ethics Committee is not required[27]. Informed consent is automatically considered signed upon completing and submitting an anonymous and voluntary questionnaire[28]. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The database for the study was obtained from the responses to the Google Forms survey, which was completed after the races. The data was collected in Excel format, so it was first imported into SPSS to perform the data analysis. The statistical analysis was conducted using SPSS version 30.0.0.

A descriptive analysis of the variables was performed, showing the mean and standard deviation for quantitative variables, and counts and percentages for categorical variables.

Results

General race outcomes

Table 1 presents, for each race, the maximum number of available spots, the number of registrations, the number of athletes starting the race, and the number of withdrawals, both in absolute terms and percentages. The highest proportion of athletes who started the race was observed in the longer and more demanding events, and similarly, the highest rate of withdrawals was in these races.

25.9% of participants were women and 74.1% were men. The highest female participation occurred in the "Vuelta al Molino de Cerler" (58%), while the lowest was in the "Gran Trail Aneto-Posets" (GTAP) (8.5%).

Seven age categories were defined (Table 2). The largest proportion of registrants fell within the 35-54 years age range: 33.6% for those aged 35–44 years, and 31.7% for those aged 45–54 years (65.3% combined). The 25–34 years category was also notable, accounting for 20.1% of the total. The extreme age groups (both younger and older participants) had much smaller proportions: 7.5% for those aged 55–64 years, 5.0% for those aged 18–24 years, 1.1% for those under 18, and 0.9% for those over 65. The youngest participant was 15 years old (Vuelta al Pico Cerler,

Table 1. Maximum places, registrations, runners who start the races and runners who dropped per each race.

Races	Maximun places	Registrations n/ (%)*	Runners n/ (%)**	Dropped n/ %***
Gran Trail A-P	350	305 (87.1)	297 (97.4)	123 (41.5)
Vuelta al Aneto	850	732 (86.1)	665 (90.9)	59 (8.9)
Marathon	1,100	993 (90.3)	893 (89.9)	29 (3.2)
Vuelta PC	1,050	767 (73)	627 (81.7)	9 (1.4)
Vuelta MC	450	464 (103.1)#	383 (82.5)	3 (0.8)
KV	150	112 (74.7)	100 (89.3)	0
Total	3,950	3,373 (85.4)	2,965 (87.9)	232 (7.8)

Caption: A-P: Aneto-Posets; Vuelta PC: Vuelta Pico Cerler; Vuelta MC: Vuelta Molino Cerler; KV: Kilómetro Vertical; n/ (%): absolute number (percentage).
*percentages of the number of places; **percentages of the number of registrations; ***percentages of the number of runners; #14 runners were admitted over the limit of places.

Table 2. NSAIDs and caffeine consumption among the runners who finished the race.

Age (years)	Surveys	NSAID n/ (%)	Caffeine n/ (%)	Both n/ (%)
Gran Trail A-P	**102**	**27 (26.5)**	**41 (40.2)**	**26 (25.5)**
<18	0	0	0	0
18-24	0	0	0	0
25-34	9	3 (11.1)	7 (17)	4 (15.4)
35-44	26	9 (33.3)	16 (39)	8 (30.8)
45-54	28	11 (40.8)	15 (36.8)	11 (42.3)
55-64	5	3 (11.1)	3 (7.2)	3 (11.5)
>65	1	1 (3.7)	0	0
Vuelta al Aneto	**187**	**29 (15.5)**	**94 (50.3)**	**49 (26.2)**
<18	0	0	0	0
18-24	3	0	3 (3.2)	1 (2.1)
25-34	30	9 (31)	16 (17)	8 (16.3)
35-44	61	8 (27.6)	30 (32)	16 (32.6)
45-54	74	9 (31)	35 (37.2)	20 (40.8)
55-64	14	2 (6.9)	10 (10.6)	4 (8.2)
>65	1	1 (3.5)	0	0
Marathon	**269**	**37 (14.1)**	**140 (52.1)**	**51 (19)**
<18	0	0	0	0
18-24	7	0	4 (2.9)	1 (1.9)
25-34	62	10 (27)	35 (25)	7 (13.8)
35-44	91	10 (27)	52 (37.1)	16 (31.5)
45-54	83	7 (18.9)	38 (27.1)	23 (45)
55-64	20	9 (24.4)	7 (5)	4 (7.8)
>65	2	1 (2.7)	4 (2.9)	0

(continue)

Table 2. NSAIDs and caffeine consumption among the runners who finished the race *(continuation)*.

Age (years)	Surveys	NSAID n/ (%)	Caffeine n/ (%)	Both n/ (%)
Vuelta PC	**124**	**13 (10.5)**	**70 (56.5)**	**14 (11.3)**
<18	0	0	0	0
18-24	10	0	4 (5.7)	1 (7.1)
25-34	27	1 (7.7)	18 (25.7)	1 (7.1)
35-44	42	5 (38.4)	20 (28.6)	8 (57.2)
45-54	34	2 (15.4)	24 (34.3)	4 (28.6)
55-64	10	5 (38.5)	4 (5.7)	0
>65	1	0	0	0
Vuelta MC	**50**	**9 (18)**	**15 (30)**	**2 (4)**
<18	5	0	2 (13.3)	1 (50)
18-24	6	2 (22.2)	3 (20)	0
25-34	8	1 (11.1)	4 (26.6)	0
35-44	9	1 (11.1)	3 (20)	0
45-54	14	2 (22.2)	2 (13.3)	0
55-64	8	3 (33.4)	1 (6.8)	0
>65	0	0	0	0
KV	**19**	**1 (5.3)**	**8 (42.1)**	**0**
<18	2	0	0	0
18-24	5	1 (100)	1 (12.5)	0
25-34	2	0	2 (25)	0
35-44	4	0	3 (37.5)	0
45-54	3	0	1 (12.5)	0
55-64	2	0	1 (12.5)	0
>65	1		0	0
Total	751	116 (15.5)	368 (49)	142 (18.9)

Caption: A-P: Aneto-Posets; Vuelta PC: Vuelta Pico Cerler; Vuelta MC: Vuelta Molino Cerler; KV: Kilómetro Vertical; NSAID: non-steroidal anti-inflammatory drug; n/(%): absolute number/ (percentage).

Vuelta al Molino de Cerler) and 14 years old (cadets) in the KV. Athletes over the age of 70 participated in the GTAP, Maratón de las Tucas, Vuelta al Pico Cerler, and Vuelta al Molino de Cerler, with some exceeding 75 years in the Maratón de las Tucas and Vuelta al Molino de Cerler.

The average age slightly varied between races, with the "Gran Trail Aneto-Posets" having the oldest participants (44.8 years). The average age for the Vuelta al Aneto was 42.8, for the Marathon 41.6, for the Vuelta al Pico Cerler 39.1, for the Vuelta al Molino de Cerler 39.2, and for the KV 38.0.

The mean race completion time for the GTAP was 27:25:35 (best time 16:26:27, worst time 37:19:23), for the Vuelta al Aneto 12:13:52 (best time 6:52:30, worst time 19:58:14), for the Maratón de las Tucas 8:30:00 (best time 4:34:07, worst time 12:42:26), for the Vuelta al Pico Cerler 3:53:51 (best time 2:03:25, worst time 5:51:30), and for the Vuelta al Molino de Cerler 1:41:32 (best time 0:54:28, worst time 2:53:19).

Surveys received

A total of 2,965 athletes participated in the races, and 751 surveys were received, representing 25.3% of the participants. Table 3 shows the number of surveys collected for each race, their relationship with the number of starters, and the distribution of responses by gender. The results show a significant difference in response rates between men and women. Among women, the highest number of surveys was recorded in the shorter races, with the Vuelta al Molino de Cerler receiving more responses from women than men.

When analyzing participation differences in the surveys between athletes who finished the race and those who withdrew, it was found that the majority of responses came from finishers. In the GTAP, 66.6% of finishers responded, in the Vuelta al Aneto 97.9%, in the Marathon 98.5%, and in the Vuelta al Pico Cerler, Vuelta al Molino de Cerler, and KV, 100% of finishers responded. In total, 710 (94.5%) of the surveyed athletes completed the race, and 41 (5.5%) withdrew, with the majority of withdrawals occurring in the GTAP (81%), particularly at the Benasque aid station, where the Vuelta al Aneto loop finishes and the Vuelta al Posets loop begins. The KV had no withdrawals.

Participant characteristics

Of the 751 survey respondents, 575 (76.6%) were male and 176 (23.4%) were female. The mean age was 41.74 ± 10.1 years, the mean weight was 69.03 ± 10.99 kg, and the mean height was 173.37 ± 8.45 cm. The average age of male participants was higher than that of female participants, as was their weight and height (Table 4).

Comparison of average times: overall, finishers, and non-finishers

These comparisons are presented in Table 5.

NSAID and caffeine consumption among finishers

A total of 258 (34.4%) athletes consumed NSAIDs, with 15.5% using only NSAIDs, and 18.9% using a combination of NSAIDs and caffeine.

Table 3. Number of surveys collected for each race and distribution of responses by gender.

Races	Starters	Surveys* n/ (%)	Men** n/ (%)	Women** n/ (%)
Gran Trail A-P	297	102 (34.4)	95 (93.1)	7 (6.9)
Vuelta al Aneto	665	187 (15.5)	162 (86.6)	25 (13.4)
Marathon	893	269 (27.1)	204 (75.8)	65 (24.2)
Vuelta PC	627	124 (16.2)	80 (64.5)	44 (35.5)
Vuelta MC	383	50 (10.8)	21 (42)	29 (58)
KV	100	19 (17)	13 (68.4)	6 (31.6)
Total	2,965	751 (22.3)	666 (88.8)	85 (11.2)

Caption: A-P: Aneto-Posets; Vuelta PC: Vuelta Pico Cerler; Vuelta MC: Vuelta Molino Cerler; KV: Kilómetro Vertical; n (%): absolute number (percentage);
*Collected surveys; **Distribution of responses by gender.

Table 4. Participant demographics.

Variable	Average ±SD	Median	IQ range	Lower-upper limit
Total age (years)	41.74 ± 10.1	42	35-49	14-74
Male age	42.35 ± 9.92	43	35-7.45	14-72
Female age	39.77 ± 10.45	41	33-49	14-72
Total weight (kg)	69.03 ± 10.99	70	62-76	43-115
Male weight	72.67 ± 8.37	72	67-78	43-115
Female weight	56.54 ± 6.43	56	52-60	43-75
Total height (cm)	173.37 ± 8.45	174	168-180	148-198
Male height (cm)	176.65 ± 7.91	176	172-180	158-198
Female height (cm)	163.25 ± 5.91	163	160-167	148-178

Caption: SD: standard deviation; IQ: interquartile. kg: kilograms; cm: centimeters.
Note: the lower limit of 14 years old correspond to 3 male cadets and a female cadet who participated in KV race.

Table 5. Comparison of average times: overall, finishers and non-finishers.

Races	Average time (AT) general h:min:seconds	AT finishers h:min:seconds	AT non-finishers h:min:seconds
Gran Trail A-P	27:25:35	27:51:38	13:56:56
Vuelta al Aneto	12:13:52	12:15:06	10:33:33
Marathon	8:30:00	8:36:29	5:07:25
Vuelta PC	3:53:51	3:55:09	NA
Vuelta MC	1:41:32	1:47:32	NA

Caption: A-P: Aneto-Posets; Vuelta PC: Vuelta Pico Cerler; Vuelta MC: Vuelta Molino Cerler; AT: average time; h:min:seconds: hours minutes seconds; NA: does not appear.
Note: in Vuelta al pico Cerler race only 9 athletes withdraw and in Vuelta al Molino race 3.

The highest consumption was recorded in the GTAP (52% of respondents), followed by the Vuelta al Aneto (41.7%). The age group between 35 and 54 years had the highest consumption in all races, except in the KV (Table 2). Ibuprofen was the most commonly used NSAID (69.3%), followed by dexketoprofen (18.7%). Of the athletes using ibuprofen, 54.7% consumed the 400 mg dose, while 45.3% consumed the 600 mg dose. Further results on NSAID consumption are presented in Table 6.

A total of 510 (67.9%) athletes consumed caffeine, with 368 (49%) using it alone and 142 (18.9%) combining it with NSAIDs. The highest caffeine consumption was seen in the Vuelta al Aneto (76.5%), followed by the Vuelta al Pico Cerler (67.8%) and the Gran Trail Aneto-Posets (65.7%). Similar to NSAIDs, athletes in the 35–54 age group were the highest consumers in all races, including the KV (Table 2). Further results on caffeine consumption are shown in Table 6.

Clinical symptoms experienced during the races

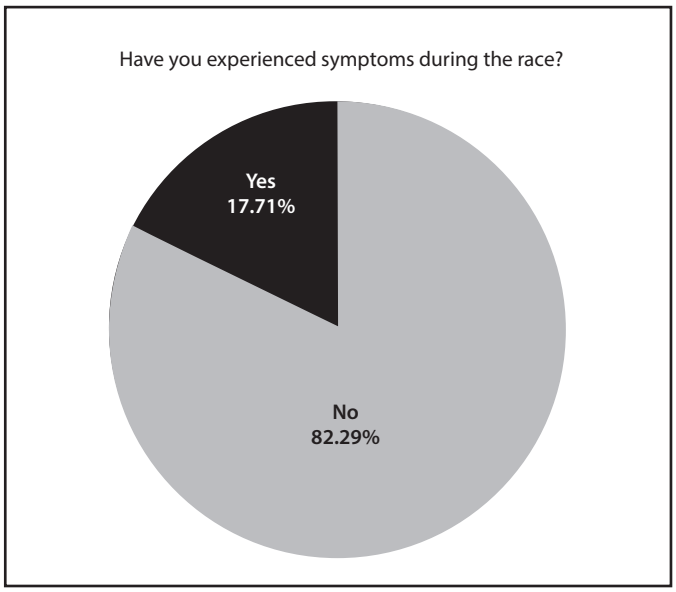
During the races, 133 (17.7%) participants reported experiencing symptoms (Figure 1). Of these, 62 (46.6%) experienced gastrointestinal symptoms (nausea, vomiting, diarrhea, and related pain), which were the most common. Neurological symptoms (dizziness, headaches, distorted vision, sleepiness, visual hallucinations, and vertigo) occurred in 27 participants (20.3%), musculoskeletal symptoms (injuries, trauma, muscle pain, muscle cramps, and osteoarticular pain) in 19 (14.3%), cardiac symptoms (precordial pain, palpitations) in 10 (7.5%), 6 (4.5%) exhibited multiple symptoms, and 9 (6.8%) had other symptoms, mainly fatigue, heat, cold, blisters on the feet, or negative thoughts.

Table 6. NSAID and caffeine consumption.

Nsaid consumption	Drug n/ (%)	Ibuprofen 179 (69.4)	Dexketoprofen 50 (19.4)	Others 29 (11.2)	-
Ibuprofen consumption	Filing n/ (%)	400 mg 98 (57.7)	600 mg 81 (45.3)	-	-
Consumption by gender	n/(%) Total* n/(%) Género n: 258**	M: 575 (76.6) 199 (34.6) 199 (77.1)	W:176 (23.4) 59 (33.5) 59 (22.9)	-	-
Race consumption	n : 751* n/ (%) n: 258** n/ (%)	Before 104 (13.8) 104 (40.3)	During 136 (18.1) 136 (52.7)	After 130 (17.3) 130 (50.4)	-
Ibuprofen consumption (milligrams)	n :179***	Average ± SD 782.1 ± 447.9	Median 600	IQ range 440-1,200	Lower-upper limit 400-2,800
Caffeine consumption	n/ (%)	Yes 510 (67.9)	No 241 (32.1)	-	-
Consumption by gender	n/ (%) Total# n/ (%) Gender n: 510##	M: 412 (54.9) 412 (71.7)	W: 98 (13.1) 98 (55.7)	-	-
Race consumption	n: 751# n/(%) n: 510## n/(%)	Before 473 (63) 473 (92,7)	During 506 (67,3) 506 (99,2)	-	-
Caffeine consumption (miligrams)	n: 510##	Average ± SD 291.7 ± 546.3	Median 200	IQ range 100-350	Lower-upper limit 25-9,000

Caption: n/ (%): absolut number (percentage); mg: milligrams; M. men; W: women; SD: standard deviation; IQ: interquartile range.
*: total number of received surveys; **: number of athletes who consumed NSAID; ***: number of athletes who consumed ibuprofen; #: total number of received surveys; ##: athletes who consumed caffeine.
Note: regarding NSAID consumption in the race (n: 258), it must be noted that there were athletes who consumed in all possibilities.

Figure 1. Experiencing symptoms during the races.



Discussion

Regular physical activity presents several benefits for cardiovascular health, improves parts of the innate immune system and reduces the risk of infection[6,27]. Moderate physical activity is also known to be beneficial, preventing many lifestyle-related diseases and reducing all-cause mortality[19].

In general, aerobic exercise is associated with long-term benefits for the gastrointestinal system, such as reversal of non-alcoholic fatty liver disease and lower rates of colorectal cancer[28]. These findings may be due in part to the beneficial effects of exercise on the gut biome[29]. Changes in the gut biome are often associated with improvements in microbiota diversity, inflammatory markers, metabolic profiles and immune responses[30].

As a result, endurance and ultra-endurance MR have recently become more popular and participation has increased[6]. However, it's also important to acknowledge that greater participation in these races comes with a higher risk of adverse health effects and potential long-term conditions, which remain unknown and require further research based on the current evidence[7].

Participation in endurance sports has steadily increased among youth (<19 years), masters (>35 years), and female athletes in recent years. Each group requires special consideration due to their heightened risk of long-term health issues[7,31]. For instance, young endurance athletes are physiologically less mature and may be more prone to exercise-related injuries compared to older, more experienced competitors. Intense physical activity at a young age can place excessive stress on a developing body, potentially leading to long-term health concerns[32,33]. Similarly, elite athletes with pre-existing conditions may face an increased risk, as prolonged training and competition could exacerbate underlying health issues[34]. Female athletes also require particular attention due to the complex relationship between menstrual function and bone health[35].

NSAIDs are widely used in sports medicine, but there is a high rate of non-prescribed use and limited awareness of their side effects[36,37]. This study found that 34.4% of athletes used NSAIDs, with the Gran Trail A-P having the highest usage. Previous research suggests that between 35% and 75% of ultramarathon runners use NSAIDs during competition[11,17], aligning with these findings. Previously published studies have also shown that NSAID use is more common among older age groups[7], which is consistent with the results of this study.

NSAIDs are among the most used drugs for musculoskeletal pain and inflammation. However, their use is not always beneficial in athletes, as excessive or inappropriate use of these drugs during MR could pose a potential health risk[38].

Ibuprofen, the most commonly used NSAID in GTTAP, belongs to the propionic acid derivative group, a widely available and commonly used class of NSAIDs in ultramarathon events[21,39]. Its use provides antipyretic, analgesic, and anti-inflammatory effects[40]. However, the safety of NSAID use during strenuous exercise is debated due to its association with increased intestinal permeability and enhanced absorption of endotoxins into the bloodstream, potentially leading to inflammation and gastrointestinal symptoms[41]. Notably, gastrointestinal issues such as nausea, vomiting, abdominal pain, and diarrhea are prevalent among ultrarunners. These symptoms can contribute to severe dehydration, which, when combined with the nephrotoxic effects of ibuprofen, may compromise renal function[18]. While NSAIDs reduce cytokine production and suppress the inflammatory response[42] in damaged tissues, current data suggest that athletes who complete ultra-endurance mountain races have higher concentrations of markers associated with injury, inflammation, muscle damage, kidney damage and cardiac damage that persist for more than 72 hours post-race, depending on the distance covered[6,18]. Importantly, ibuprofen does not mitigate muscle damage during competition[18], nor does it reduce soreness caused by muscle injury. Furthermore, its prophylactic use has no proven benefit on physical performance[21], despite the common misconception that it enhances endurance[38]. These observations suggest that MR athletes should be cautious with non-medically justified use of NSAIDs due to the side effects described and the limited evidence for widespread beliefs[43,44].

Caffeine (1,3,7-trimethylxanthine) is a widely used supplement among athletes across various sports, with 74% of elite athletes consuming it as an ergogenic aid before or during competition. Its use is particularly prevalent in endurance sports[45]. It is one of the most consumed sports performance-enhancing substances due to its well-established ergogenic effects in a variety of exercise situations[46].

The performance benefits of caffeine are attributed to multiple physiological mechanisms, including increased central nervous system stimulation, enhanced catecholamine release, and improved skeletal muscle contractility[47]. The benefits of caffeine in sport may also be achieved through psychobiological responses such as the 'caffeine placebo phenomenon'[48]. Moderate doses (3–6 mg/kg body weight) have been shown to provide slight improvements in endurance performance under conditions of heat and altitude, as well as enhance cognitive function in sleep-deprived states[49] relevant to events like the Gran Trail A-P, where finish times often exceed 24 hours. Although caffeine appears to enhance physical performance in both trained and untrained athletes[49], caffeine is unlikely to give athletes a significant advantage over

their competitors, but may prevent them from being at a disadvantage against competitors who are also using caffeine supplements[50]. While its effects on short-term, high-intensity exercise remain inconsistent[45], it is still recommended for such activities[51]. However, very high doses of caffeine (≥9 mg/kg) are associated with a high incidence of adverse effects and do not have a major ergogenic effect[52]. Furthermore, the physiological effects of caffeine have significant individual variability and are influenced by factors such as genetics, differences in gut microbiota, hydration, gender and training level[52].

Caffeine, due to its diuretic effect at doses ≥6 mg/kg, poses a risk of dehydration and alters the water-electrolyte balance[52]. This risk is further compounded by the high prevalence of gastrointestinal symptoms among endurance athletes[11-13], as observed in the results, which can impair proper hydration. Additionally, gastrointestinal complications induced by NSAIDs[41], their nephrotoxic effects[18], the physiological stress of endurance racing, natural dehydration, and muscle damage—including rhabdomyolysis[15,16]—can contribute to the development of acute renal failure[18-20]. The lethal dose of caffeine is 10 g[24] cases of rhabdomyolysis with acute renal failure have been reported at doses as low as 400 mg (4 mg/kg)[53]. The study results indicate that the mean caffeine dose consumed was below 300 mg; however, the standard deviation was high (546 mg) due to a maximum recorded intake of 9 g. Athletes should be aware of the risks associated with excessive caffeine consumption, as even mild overdose can lead to restlessness, nausea, vomiting, rhabdomyolysis, palpitations, tachycardia, and renal failure. More severe intoxication may result in seizures, hypokalemia, hyperglycemia, hypotension, renal failure, ventricular arrhythmias, and fatal ventricular fibrillation[23-25].

The main limitation of this study is the sample size, as well as potential bias introduced by participant dropout and a lack of interest in responding to the survey. Additionally, some participants may not have accurately reported their caffeine intake. However, a key strength of this study is the ability to analyze six different races within the GTTAP, covering a range of distances from ultra-endurance and endurance events to shorter, high-intensity races such as the KV. Furthermore, the reported symptomatology likely reflects real-world conditions, as most respondents' finish times closely matched the overall race averages, while those who dropped out had been running for extended durations.

Conclusions

NSAIDs and caffeine, being easily accessible drugs, are widely consumed in TR. Ibuprofen is the most commonly used NSAID, while caffeine has a higher consumption rate than NSAIDs. Both substances, like TR, can have adverse health effects, and their use is more prevalent among older age groups. It is essential to develop informational campaigns about the health risks associated with each of these substances, particularly when consumed in excess or in combination. Further research should be conducted to assess their potential long-term consequences.

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Conflict of interest

The authors do not declare a conflict of interest.

Bibliography

1. Pradas F, Falcón D, Peñarrubia-Lozano C, Toro-Román V, Carrasco L, Castellar C. Effects of ultratrail running on neuromuscular function, muscle damage and hydration status. Differences according to training level. *Int J Environ Res Public Health*. 2021;18:5119.
2. Rochat N, Gesbert V, Seifert L, Hauw D. Enacting phenomenological gestalts in ultra-trail running: an inductive analysis of trail runners' courses of experience. *Front Psychol.* 2018;9:2038.
3. Ramos-Campo DJ, Ávila-Gandía V, Alacid F, Soto-Méndez F, Alcaraz PE, López-Román *et al.* Muscle damage, physiological changes, and energy balance in ultra-endurance mountain-event athletes. Appl Physiol Nutr Metab. 2016;41:872-78.
4. Hodgson LE, Walter E, Venn RM, Galloway R, Pitsiladis Y, Sardat F, *et al.* Acute kidney injury associated with endurance events-is it a cause for concern? A systematic review. *BMJ Open Sport Exerc Med.* 2017;3:e000093.
5. Tidmas V, Brazier J, Bottoms L, Muniz D, Desai T, Hawkins J, *et al.* Ultra-endurance participation and acute kidney injury: a narrative review. *Int J Environ Res Public Health*. 2022;19:16887.
6. Rubio-Arias JÁ, Ávila-Gandía V, López-Román FJ, Soto-Méndez F, Alcaraz PE, Ramos-Campo DJ. Muscle damage and inflammation biomarkers after two ultra-endurance mountain races of different distances: 54 km vs 111 km. Physiol Behav. 2019;205:51-7.
7. Scheer V, Tiller NB, Doutreleau S, Khodaee M, Knechtle B, Pasternak A *et al.* Potential long-term health problems associated with ultra-endurance running: a narrative review. *Sports Med.* 2022;52:725-40.
8. Kim HJ, Lee YH, Kim CK. Biomarkers of muscle and cartilage damage and inflammation during a 200 km run. *Eur J Appl Physiol*. 2007;99:443-7.
9. Del Coso J, Salinero JJ, Abián-Vicen J, González-Millán C, Garde S, Vega P, *et al.* Influence of body mass loss and myoglobinuria on the development of muscle fatigue after a marathon in a warm environment. *Appl Physiol Nutr Meta*b. 2013;38:286-91.
10. Fridén J, Sjöström M, Ekblom B. Myofibrillar damage following intense eccentric exercise in man. *Int J Sports Med.* 1983;4:170-6.
11. Hoffman MD, Fogard K. Factors related to successful completion of a 161-km ultra-marathon. *Int J Sports Physiol Perform*. 2011;6:25-37.
12. Stuempfle KJ, Hoffman MD. Gastrointestinal distress is common during a 161-km ultramarathon. *J Sports Sci.* 2015;33:1814-21.
13. Wardenaar FC, Dijkhuizen R, Ceelen IJ, Jonk E, de Vries JH, Witkamp RF, *et al*. Nutrient intake by ultramarathon runners: can they meet recommendations? *Int J Sport Nutr Exerc Metab.* 2015;25:375-86.
14. Karhu E, Forsgård RA, Alanko L, Alfthan H, Pussinen P, Hämäläinen E, *et al.* Exercise and gastrointestinal symptoms: running-induced changes in intestinal permeability and markers of gastrointestinal function in asymptomatic and symptomatic runners. *Eur J Appl Physiol.* 2017;117:2519-26.
15. Gerth J, Ott U, Fünfstück R, Bartsch R, Keil E, Schubert K, *et al*. The effects of prolonged physical exercise on renal function, electrolyte balance and muscle cell breakdown. *Clin Nephrol.* 2002;57:425-31.
16. Kao WF, Hou SK, Chiu YH, Chou SL, Kuo FC, Wang SH, *et al.* Effects of 100-km ultramarathon on acute kidney injury. *Clin J Sport Med*. 2015;25:49-54. Erratum in: *Clin J Sport Med.* 2016;26:171.
17. Lipman GS, Shea K, Christensen M, Phillips C, Burns P, Higbee R, *et al*. Ibuprofen versus placebo effect on acute kidney injury in ultramarathons: a randomised controlled trial. *Emerg Med J.* 2017;34:637-42.
18. de Souza RF, de Matos DG, Ferreira ARP, Chilibeck P, Barros NA, Oliveira AS, *et al.* Effect of ibuprofen on muscle, hematological and renal function, hydric balance, pain, and performance during intense long-distance running. *J Strength Cond Res*. 2020;34:2076-83.
19. Scheer V. Severe kidney injury after a 110-km trail race. *Cureus.* 2020;12:e7814.
20. Page AJ, Reid SA, Speedy DB, Mulligan GP, Thompson J. Exercise-associated hyponatremia, renal function, and nonsteroidal antiinflammatory drug use in an ultraendurance mountain run. *Clin J Sport Med.* 2007;17:43-8.
21. de Souza RF, de Matos DG, Lopes Dos Santos J, Andrade Lima C, Reis Pires Ferreira A. Moreno G, *et al.* Effects of ibuprofen during 42-km trail running on oxidative stress, muscle fatigue, muscle damage and performance: a randomized controlled trial. *Res Sports Med*. 2024;32:400-10.
22. Rojas-Valverde D, Olcina G, Gutiérrez-Vargas R, Crowe J. Heat strain, external workload, and chronic kidney disease in tropical settings: are endurance athletes exposed? *Front Physiol*. 2019;10:1403.

23. Koide N, Sato N, Kondo D, Hirose Y. Caffeine overdose complicated by acute kidney injury despite mild creatine kinase elevation. *Case Rep Acute Med.* (revista electronica) 2020 JanApr (consulted: 16/02/2025). Available in: https://doi.org/10.1159/000507181.
24. Campana C, Griffin PL, Simon EL. Caffeine overdose resulting in severe rhabdomyolysis and acute renal failure. *Am J Emerg Med*. 2014;32:111.e3-4.
25. Eichner ER. Updates on team rhabdomyolysis, caffeine fatalities, and heat cramping. *Curr Sports Med Rep*. 2015;14(6):423-4.
26. Iyer PS, Yelisetti R, Miriyala V, Siddiqui W, Kaji A. A remarkable case of rhabdomyolysis associated with ingestion of energy drink 'neon volt'. *J Community Hosp Intern Med Perspect.* 2016;6:32528.
27. Universidad de Navarra. Comité de Ética de la investigación. Hoja de información y consentimiento informado. Investigaciones en ciencias sociales. Versión 3.0. (consultado 27/05/2025). Disponible en: https://www.unav.edu/documents/10162/33107088/hoja-de-informacion-y-consentimiento-informado-investigacion-en-ciencias-sociales.pdf/671603ec-8ae4-d140-9b56-aeb08d49e240?t=1731671927503.
28. Canimas Brugué J, Bonmatí Tomàs A. Guía de los aspectos éticos a valorar de los proyectos de investigación con personas o con datos personales. Girona. Universitat de Girona; 2021 (1ª ed.) p.28.
29. Gleeson M. Immune function in sport and exercise. *J Appl Physiol* (1985). 2007;103:693-9.
30. Martin D. Physical activity benefits and risks on the gastrointestinal system. *South Med J.* 2011;104:831-7.
31. Sohail MU, Yassine HM, Sohail A, Thani AAA. Impact of physical exercise on gut microbiome, inflammation, and the pathobiology of metabolic disorders. *Rev Diabet Stud.* 2019;15:35-48.
32. Grosicki GJ, Durk RP, Bagley JR. Rapid gut microbiome changes in a world-class ultramarathon runner. *Physiol Rep*. 2019;7:e14313.
33. Lepers R, Stapley PJ. Master athletes are extending the limits of human endurance. *Front Physiol.* 2016;7:613.
34. Scheer V, Sousa CV, Valero D, Knechtle B, Nikolaidis PT, Valero E. Retraction: a descriptive study on health, training and social aspects of adults that participated in ultra endurance running as youth athletes. *J Sports Med Phys Fitness.* 2020.
35. Scheer V, Costa RJS, Doutreleau S, Knechtle B, Nikolaidis PT, Roberts WO, *et al.* Recommendations on youth participation in ultra-endurance running events: a consensus statement. *Sports Med.* 2021;51:1123-35..
36. Tso J, Kim JH. Master endurance athletes and cardiovascular controversies. *Curr Sports Med Rep.* 2020;19:113-8.
37. Nattiv A, Loucks AB, Manore MM, Sanborn CF, Sundgot-Borgen J, Warren MP; American College of Sports Medicine. American College of Sports Medicine position stand. The female athlete triad. *Med Sci Sports Exerc.* 2007;39:1867-82.
38. Paoloni JA, Milne C, Orchard J, Hamilton B. Non-steroidal anti-inflammatory drugs in sports medicine: guidelines for practical but sensible use. *Br J Sports Med.* 2009;43:863-5.
39. Gorski T, Cadore EL, Pinto SS, da Silva EM, Correa CS, Beltrami FG, *et al.* Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med.* 2011;45:85-90.
40. Chlíbková D, Ronzhina M, Nikolaidis PT, Rosemann T, Knechtle B. Non-steroidal anti-inflammatory drug consumption in a multi-stage and a 24-h mountain bike competition. *Front Physiol.* 2018;9:1272.
41. Torjesen I. Ibuprofen can mask symptoms of infection and might worsen outcomes, says european drugs agency. *BMJ.* 2020;369:m1614.
42. Lima FD, Stamm DN, Della Pace ID, Ribeiro LR, Rambo LM, Bresciani G, *et al.* Ibuprofen intake increases exercise time to exhaustion: a possible role for preventing exercise-induced fatigue. *Scand J Med Sci Sports.* 2016;26:1160-70.
43. Ashton T, Young IS, Davison GW, Rowlands CC, McEneny J, Van Blerk C, *et al.* Exercise-induced endotoxemia: the effect of ascorbic acid supplementation. *Free Radic Biol Med.* 2003;35:284-91.
44. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. *Inflammopharmacology.* 2009;17:275-342.
45. Da Silva E, Pinto RS, Cadore EL, Kruel LF. Nonsteroidal anti-inflammatory drug use and endurance during running in male long-distance runners. *J Athl Train*. 2015;50:295-302.
46. Brennan R, Wazaify M, Shawabkeh H, Boardley I, McVeigh J, Van Hout MC. A Scoping review of non-medical and extra-medical use of non-steroidal anti-inflammatory drugs (NSAIDs). *Drug Saf.* 2021;44:917-928.
47. Del Coso J, Muñoz G, Muñoz-Guerra J. Prevalence of caffeine use in elite athletes following its removal from the world anti-doping agency list of banned substances. *Appl Physiol Nutr Metab.* 2011;36:555-61.
48. Pickering C, Grgic J. Caffeine and exercise: what next? *Sports Med.* 2019;49:1007-30.
49. Cristina-Souza G, Santos PS, Santos-Mariano AC, Coelho DB, Rodacki A, DE-Oliveira FR, *et al.* Caffeine increases endurance performance via changes in neural and muscular determinants of performance fatigability. *Med Sci Sports Exerc.* 2022;54:1591-1603.
50. Wang Z, Qiu B, Gao J, Del Coso J. Effects of caffeine intake on endurance running performance and time to exhaustion: a systematic review and meta-analysis. *Nutrients.* 2022;15:148.
51. Jagim AR, Harty PS, Tinsley GM, Kerksick CM, Gonzalez AM, Kreider RB, *et al.* International society of sports nutrition position stand: energy drinks and energy shots. *J Int Soc Sports Nutr.* 2023;20:2171314.
52. Southward K, Rutherfurd-Markwick KJ, Ali A. Correction to: The effect of acute caffeine ingestion on endurance performance: a systematic review and meta-analysis. *Sports Med.* 2018;48:2425-41. Erratum for: *Sports Med*. 2018;48:1913-28.
53. Guest NS, VanDusseldorp TA, Nelson MT, Grgic J, Schoenfeld BJ, Jenkins NDM, *et al.* International society of sports nutrition position stand: caffeine and exercise performance. *J Int Soc Sports Nutr.* 2021;18:1.
54. Lowery LM, Anderson DE, Scanlon KF, Stack A, Escalante G, Campbell SC, *et al.* International society of sports nutrition position stand: coffee and sports performance. *J Int Soc Sports Nutr.* 2023;20:2237952.
55. Tinawi M. Severe rhabdomyolysis due to strenuous exercise with a potential role of a high-caffeine energy drink. *Cureus.* 2022;14:e20867.