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# PREVALENCE OF ACUTE MOUNTAIN SICKNESS IN THE PYRENEES

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## 1 Abstract

**Background:** Acute mountain sickness (AMS) is the most common condition of High-Altitude Illnesses (HAI). The prevalence ranges between 15% and 80% depending on the absolute altitude reached, speed of ascent, and individual susceptibility. However, there is a lack of information regarding AMS at moderate to high altitudes (2,500-3,500m); and, even less, in the Pyrenees.

**Objective:** The main goals of the present study were to determinate the prevalence and risk factor for AMS in the Pyrenees.

**Methods:** A cross-sectional study that includes mountaineers who have climbed a mountain with a height greater than 2,500m in the area of the Pyrenees. Between July and August 2019 data were collected using a questionnaire including sociodemographic, medical history and activity information. The diagnosis of AMS was based on the Lake Louise Score 2018 (LLS).

**Results:** The study included 437 participants. One hundred and seventeen met diagnostic criteria of AMS, establishing a prevalence of 26.6% (95% confidence interval: 22.6% to 30.9%). The most common AMS symptom was headache, followed by fatigue or weakness, gastrointestinal symptoms and dizziness. Most of those affected by AMS had mild (88%) or moderate (12%) symptoms. In an adjusted multivariate analysis, heavy perceived exertion, bad physical condition and previous history of HAI were independent risk factors for AMS.

**Conclusions:** One fourth of climbers in the Pyrenees experienced mild or moderate AMS. Previous history of HAI and other modifiable risk factors such as physical exertion and physical condition were strong predictors of AMS. Educational/informational programs for individuals planning climbing to high altitudes in the Pyrenees would be desirable.

**Key words:** acute mountain sickness; AMS; altitude illness; prevalence; heavy exertion; risk factors; high altitude illness; physical condition;

## 2 Abbreviations

<b>AMS</b>	Acute Mountain Sickness
<b>BMI</b>	Body Mass Index
<b>CBF</b>	Cerebral Blood Flow
<b>CI</b>	Confidence Interval
<b>COPD</b>	Chronic Obstructive Pulmonary Disease
<b>CV</b>	Cardiovascular
<b>HACE</b>	High Altitude Cerebral Edema
<b>HAI</b>	High Altitude Illness
<b>HAPE</b>	High-Altitude Pulmonary Edema
<b>LLS</b>	Lake Louis Score
<b>m</b>	Meters
<b>NSAIDs</b>	Nonsteroidal anti-inflammatory drugs
<b>OSAS</b>	Obstructive Sleep Apnea Syndrome
<b>WHO</b>	World Health Organization

### **3 Introduction**

#### **3.1 Definition of High-altitudes illness**

High-altitude illness (HAI) is a term used for different pathology that the unacclimatized individual may develop when is exposed to hypoxia at high altitude (>2,500m). This includes three different conditions:

- **Acute Mountain Sickness (AMS):** unspecific syndrome that includes headache, dizziness, fatigue, nauseas...
- **High-Altitude Cerebral Edema (HACE):** potentially mortal illness characterized with ataxia, altered mental status and reduced consciousness.
- **High-Altitude Pulmonary Edema (HAPE):** typical early symptoms are exertional dyspnea, dry cough and reduced exercise performance. This is also a potentially mortal illness.

AMS and HACE can reflect parts of a continuum of the same condition, being HACE the end of the phase. (1)

The **classification of altitude levels** (Annex 1. Classification of altitude levels)(2) can be summarized as low altitude (500-2,000m), moderate altitude (2,000-3,000m), high altitude (3,000-5,500m) and extreme altitude (>5,500m).

#### **3.2 Epidemiology of High-Altitude Illness**

Every year, the number of people visiting destinations over 2,500m is increasing and that means that there are more individuals at risk to suffer AMS. (1) (3)

AMS is by far the most common HAI. AMS usually occurs at 2,000-2,500m or above, within the initial 4–6 hours after the ascent. Its incidence and severity increase with altitude. Its reported prevalence ranges from 8% to 25% at 2,500-3,000m and from 40% to 60% at 4,500. (2)

Studies conducted in Nepal, Aconcagua, Kilimanjaro, Mt Fuji and the Alps show that AMS prevalence ranges from 9% to 77.3%, with a higher prevalence at higher altitudes (4). See Table 1.



The reported prevalence of AMS varies widely according to different ascent profiles. For example, in Mount Kilimanjaro, the prevalence of AMS was 9% at altitudes of 2,743m, 44% at 3,760 and 58% at 4,730m (5). In Aconcagua, was as high as 75% at 4,356m (6).

*Table 1. Prevalence of AMS in different studies*

Author	Location	Altitude (m)	AMS
Mairer (3)	Alps	2,220	6.9%
		2,500	9.1%
		2,800	17.4%
		3,500	38.0%
Karinen (5)	Kilimanjaro	2,743	9%
		3,760	44%
		4,730	58%
Vardy (7)	Nepal	3,000-4,000	10%
		4,000-4,500	15%
		4,500-5,000	51%
Van Roo (6)	Aconcagua	4,365	77.3%
Horiuchi (8)	Mt Fuji	3,776	29.5%

Meanwhile HACE and HAPE are rare, with an estimated incidence of 0.1-4%, but require a fast recognition because are potentially mortal. These appears in higher altitudes, HAPE greater than 3,000m and HACE greater than 4,000m (9) (1).

The most commonly described **risk factors** are the following: (1)(4)(10)(11)

- **Genetics and biochemical factors**
- **Rate of ascent:** ascending at greater than **500m a day** above the level of 3,000m
- **Previous history** of HAI
- **Reached altitude**
- **Lack of acclimatization**
- **Residence** at an altitude **below 800m**
- **Heavy exertion** upon arrival at altitude

- **Gender:** men and women seem equally vulnerable to AMS (3,4,7). Although some studies conclude that women's have a higher risk to develop AMS compared with men (12).
- **Age:** some studies show a decreased risk of AMS among those 50 to 60 years or older and may be greater risk in younger athletes, particularly males for strenuous exertion. On the other hand, one meta-analysis suggests that there is no association between age and the risk of AMS (7,13,14).
- **Medical conditions:** Certain preexisting **cardiopulmonary conditions** such as Chronic Obstructive Pulmonary Disease (COPD), **obesity** and history of **migraine**, reported higher risk. No association between asthma or anemia have been reported. Although must be remembered, hypoxic environments exacerbate the sickle cell disease.
- **Substances:** there is no evidence that tobacco and alcohol and may increase the risk of suffer AMS. There are different studies with opposite conclusions and a deeply review should be made. (9)(15)

The frequency and intensity of AMS, however, not only depend on the above causes, but also on the physiological vulnerability of the patient (16).

The risk to develop HAI can be classified as low, moderate or high risk, according to the history of HAI, the ascending rate, the altitude reached and the rapid ascend(17). (Annex 2. Risk of HAI).

### **3.3 Physiopathology Acute Mountain Sickness**

Although several aspects of this pathophysiology remain unclear, AMS and HACE are generally considered to represent two points with the same underlying pathophysiology along a single spectrum of disease and that **AMS can progress to fatal HACE** (1).

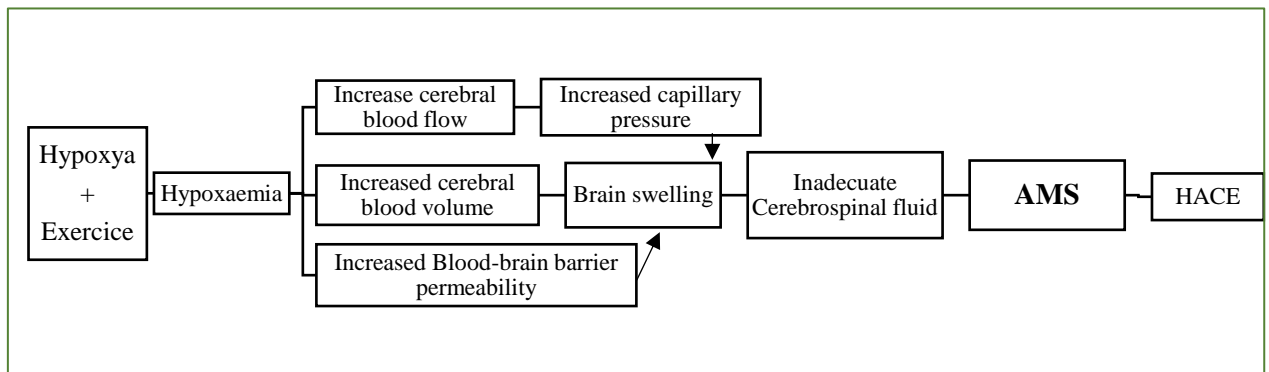
At higher altitude, **barometric pressure diminishes** and, therefore, drop the partial pressure of oxygen resulting in hypobaric hypoxia. There are different variables that decreases the barometric pressure such as lower temperature, higher latitude and inclement weather. Although the most important variable is the altitude, that becomes physiologically significant at elevations over 2,000-2,500m. (9)

The **hypobaric hypoxia** represents the initial cause of HAI. During athletic or work activities, the tissue oxygen demands are high, and if we add the reduction in the pressure gradient and available oxygen for the altitude, can lead to tissue hypoxia. Also, there is an impaired gas exchange due to interstitial pulmonary edema, fluid retention and increased metabolism. (18)

This hypobaric hypoxia triggers a series of physiological responses. One of these adaptation processes, is the increase of the heart and respiratory frequencies, which leads to a certain degree of respiratory alkalosis that other organs such as the kidney should try to compensate for. In most cases, these help the individual tolerate and adapt to the low oxygen condition. However, in other cases, maladaptive responses occur, that in turn cause one of the three form of HAI. (19)

When the hypoxemia is more severe, it might involve a greater **increase in cerebral blood** flow (CBF), also an increase in vascular permeability through a higher oxidative stress, low-grade inflammation or increase hypoxia-inducible transcription factor dependent (VEGF)(20). Figure 1. Physiopathology of AMS-HACE

*Figure 1. Physiopathology of AMS-HACE*



**Cerebral edema** develops following cerebral vasodilation secondary to hypoxia. It is found in neuroimaging and at autopsy in patients with severe AMS or HACE a reversible vasogenic brain edema, with characteristic T2 signal increase in the splenium of the corpus callosum and subcortical white matter. Brain herniation from severely increased the intracranial pressure is the cause of death in HACE. (1)

The **headache** appears by the change of the pressure of the blood vessels in the meninges, which stimulates the sensory fibers of the trigeminal gangly that is projected in the cortex.

These fibers are related with the vegetative symptoms such as nausea or vomiting. These process is similar to the migraine. (9)

The "**tight fit**" hypothesis suggests that it is not the amount of swelling that matters as much as the person's ability to tolerate such swelling. In other words, persons with a higher brain to cranial vault ratio (less space for the swollen brain) become more symptomatic than those with a smaller ratio (more space) but with the same degree of cerebral edema. This theory could explain the random nature of AMS and deserves further study. (1)

### **3.4 Clinical Manifestations High-Altitude Illness**

**AMS** usually presents between 4 and 24 hours after ascent to a new altitude more than 2,500m, often resolving within 2 to 3 days at a consistent altitude. Symptoms may be mild or severely debilitating:

- High altitude headache, that worsens on exertion (“hangover” feeling), is mandatory for the diagnosis. (see [Annex 3. Diagnostic criteria High-altitude headache](#)) (21)
- Dizziness, fatigue
- Anorexia, nausea, vomiting
- Disturbed sleep with frequent awakening
- Mild shortness breath with exertion
- Lightheadedness

It is important to recognize the **alert symptoms or signs** of worsening disease because it can rapidly progress to HACE or HAPE. Absolute indications for immediate descent include the following: (1)

- **Neurologic findings:** ataxia or change in consciousness, irritability, lethargy and diminished performance.
- **Signs of pulmonary edema** such as dyspnea at rest

**HACE** can develop in the following 24 hours. Is characterized by altered mental status, reduced consciousness and ataxia. AMS can progress to HACE and is potentially mortal.

**HAPE** typical early symptoms are exertional dyspnea, dry cough and reduced exercise performance. It is diagnosed when there are:

- Two of the following symptoms: dyspnea at rest, cough, decreased exercise performance or chest tightness
- Two of the following signs: crackles or wheeze on auscultation, central cyanosis, tachypnoea or tachycardia

### 3.5 Diagnosis of Acute Mountain Sickness

AMS is diagnosed **clinically** based upon the appearance of typical symptoms in a person who has recently ascended to high altitude (generally over 2,000 m).

For the diagnosis of AMS, there are no reliable objective measures. Physical examination, laboratory values, vital signs, and pulse oximetry typically change within the normal range.

There are different scoring systems for the diagnosis of AMS, including the Acute Mountain Sickness-Cerebral score, Visual Analog Scale, Chinese AMS Score or the Clinical Functional Score. (22). The Lake Louis Score (LLS) is the well-accepted standard (gold standard) for diagnosis AMS. Is the most popular questionnaire in use and it can be self-administrated.

A consensus process was established for the creation of the Original LLS and published in 1993. Since then, it has been an indispensable tool for AMS studies. Nevertheless, research has suggested in the recent year that sleep disturbance, a diagnostic criterion in the original LLS, is a separate entity from AMS.

Consequently, a **newly revised LLS** was agreed by consensus in 2018. This revised score eliminated sleep disturbance and also recommended the use of an optional AMS clinical functional score. (22)

The new score is a significant change in the field of research at high-altitude and should be the standard assessment of AMS in studies involving this condition.

The modification made in 2018 includes the items shown in Table 2 and is the one that we have applied in our study:

*Table 2. Lake Louis Score 2018*

<p>Headache</p> <ol style="list-style-type: none"> <li>0. None at all</li> <li>1. A mild headache</li> <li>2. Moderate headache</li> <li>3. Severe headache, incapacitating</li> </ol>
<p>Gastrointestinal symptoms</p> <ol style="list-style-type: none"> <li>0. Good appetite</li> <li>1. Poor appetite or nausea</li> <li>2. Moderate nausea or vomiting</li> <li>3. Severe nausea and vomiting, incapacitating</li> </ol>
<p>Fatigue and/or weakness</p> <ol style="list-style-type: none"> <li>0. Not tired or weak</li> <li>1. Mild fatigue/ weakness</li> <li>2. Moderate fatigue/ weakness</li> <li>3. Severe fatigue/ weakness, incapacitating</li> </ol>
<p>Dizziness/light-headedness</p> <ol style="list-style-type: none"> <li>0. No dizziness/ light-headedness</li> <li>1. Mild fatigue/weakness</li> <li>2. Moderate dizziness/light-headedness</li> <li>3. Severe dizziness/light-headedness, incapacitating</li> </ol>
<p>AMS Clinical Functional Score. Overall, if you had AMS symptoms, how did they affect your activities?</p> <ol style="list-style-type: none"> <li>0. Not at all</li> <li>1. Symptoms present, but did not force any change in activity or itinerary</li> <li>2. My symptoms forced me to stop the ascent or to go down on my own power</li> <li>3. Had to be evacuated to a lower altitude</li> </ol>

In the setting of a recent ascent or gain in altitude, AMS can be diagnosed when:

1. The global LLS score is **three or more points**, and
2. The **headache** score is **at least one point**.

The severity of AMS can be classified as follows:

- **Mild** AMS as 3-5 points
- **Moderate** AMS 6-9 points
- **Severe** 10-12 points

### 3.6 Differential Diagnosis of Acute Mountain Sickness

The difficulty in identifying AMS is the non-specific nature of symptoms, which climbers may assign to fatigue, migraine, spoiled meal or sleep deprivation. Moreover, most people associate it with very high altitudes such as Everest (8,848m) or Mount Kilimanjaro (5,890m).

The principal differential diagnoses to consider includes carbon monoxide poisoning, dehydration, exhaustion, hypoglycemia, hyponatremia, hypothermia (17,23) (Annex 4. Differential Diagnosis of High- Altitude Illnesses)

### 3.7 Treatment of Acute Mountain Sickness

The potential therapeutic options for AMS include the following: (24)(17)

- **Conservative treatment:** Patients with AMS should avoid further ascent, limit physical activity, and seek further care if any symptoms worsen.
- **Descent:** Descent is always effective treatment for AMS, but it is not always mandatory or not always possible for the wheatear or physically conditions.
- **Oxygen:** Supplemental oxygen enough to rise oxygen saturation >90% or to relive symptoms, can be used while waiting to initiate descent or when descent is not practical.
- **Hyperbaric therapy:** Portable, lightweight (less than 5 kg), manually inflated hyperbaric chambers are common in remote mountain clinics and on expeditions, where supplemental oxygen supplies are limited. But require constant tending by care providers and are difficult to use with claustrophobic or vomiting patients.
- **Symptomatic therapy:**
  - For headache: acetylsalicylic acid, acetaminophen and ibuprofen or other nonsteroidal anti-inflammatory drugs (NSAIDs)
  - For nausea and vomiting antiemetics such as ondansetron

**Pharmacological treatment** (1) (17,24): (Annex 5. Pharmacologic treatment and prevention of HAI)

- **Acetazolamide:** accelerates acclimatization to high altitude. It is a drug with diuretic effect and makes the urine more alkaline by the bicarbonate diuresis with resultant metabolic acidosis.
- **Dexamethasone:** Treatment with dexamethasone alleviates the symptoms of AMS but does NOT improve acclimatization.

The treatment is based upon symptom severity and patient preference:

- **Mild illness:** can be treated conservatively with acetylsalicylic acid or acetaminophen for the headache; antiemetics for the nausea; hydration (it is not a treatment per se but avoid the dehydration). If symptoms worsen or fail to improve after 1 or 2 days, descent should be initiated.
- **Moderate to severe** symptoms may require medication such as acetazolamide for mild illness, or dexamethasone for moderate-to-severe disease, supplemental oxygen or portable hyperbaric therapy and occasionally descent 500-1,000m or until the symptoms are resolved.

### 3.8 Prevention of Acute Mountain Sickness

**General approach:** (17,23,24)

- **Gradual ascent** remains the primary method for preventing all forms of HAI. Individuals who normally reside below 1,500m elevation should avoid an abrupt ascent to sleeping altitudes above 2,800m. If further ascent above 3,000m is planned, it is recommended not spending subsequent nights at elevations over 500m higher than the previous night and including a rest day for every 1,000m climbed.
- **Preacclimatization:** there are two forms of preacclimatization that may help to prevent HAI
  - o **preexposure** to higher altitudes (hypobaric hypoxia): Residing at a site above 2,500m or brief climbs to elevations over 2,500 to 3,000m in the weeks leading up to a trip to higher elevation.
  - o **environment** that simulate high altitude (normobaric hypoxia): the intermittent normobaric hypoxic exposure with devices like face mask or sealed tents that allows to decrease the percentage of inhaled oxygen



- **Education:** individuals with a history of HAI or cardiopulmonary disease should be advised of their increased risk for developing HAI. Also educating patients about the early symptoms and signs of HACE and HAPE can be lifesaving.
- **Alcohol and sedative-hypnotics** use should be avoided during acclimatization because causes depress respiratory function.
- **Diet and hydration:** high carbohydrate diet can reduce the incidence of HAI, but data are not conclusive. Maintenance of adequate hydration is important because symptoms of dehydration can mimic those of AMS.

### **Pharmacologic prophylaxis:**

The only **indications** of prophylactic medications are all the patients at high-moderate risk of developing HAI (Annex 2. Risk of HAI). This includes those with a known predilection for HAI despite gradual ascent, and those who must ascend rapidly for convenience (ie, tourists traveling to mountain resort) or work (ie, rescue and military personnel).

The preferred prophylactic medication is **acetazolamide**, but **dexamethasone** is also a reasonable option, but is reserved in very high-risk situations like circumstances of rapidly ascent over 3.000m because it is relatively rapid acting, highly effective, and does not depend upon acclimatization for effect. An example is the military or search and rescue personnel being airlifted.

**NSAIDs** such as acetylsalicylic acid and ibuprofen, have been shown to prevent headache on ascent to high altitude, but it is unclear whether these medications would be useful as prophylaxis or treatment because the limitations on trials. (17,24)

**Ginkgo biloba** is a complex herbal extract preparation, with many active ingredients. While some small studies suggest that ginkgo biloba is effective at reducing the symptoms of AMS in adults, larger trials have failed to demonstrate benefit. (17,24,25).

Chewed coca leaves, coca tea, and other coca-derived products are commonly recommended for travelers in the Andes but they utility in prevention of HAI has never been studied.(17,24)

## **4 Study Justification**

AMS usually manifest with headache, nausea, vomiting, fatigue, dizziness and weakness. These symptoms can be low to severe debilitating. There are non-specific symptoms, which climbers may assign to fatigue or sleep deprivation. (1)

Furthermore, if we add to these symptoms the inherent risk of the mountain, the difficulty of diagnosing due to poor knowledge, and the progression to HACE, results a potentially mortal pathology (17).

Every year, millions of visitors travel to high altitudes, and, with the increase in adventure trips and tourism, the number of individuals of all ages are climbing, hiking and skiing to altitudes above 3,000m and even higher than 5,500m, is increasing (4). They usually not have any prior acclimatization, being at risk of AMS. Even professional mountain climbers o rescue workers are at risk. Little information exists on the frequency and severity of the disorder in the general population at moderate to high altitudes, yet there is a large population at risk (24).

High-Altitude Illness research is often focused on HAPE/HACE or AMS progression with most altitude research being observational studies of trained alpinists at high (>3,000m) to extreme altitudes (>5,500m).

Therefore, relatively little is known about the prevalence of AMS at moderate to high altitudes (around 3,000 m) in nontrained visitors to altitudes higher than where they reside. Even less studies have been performed in our environment, the Pyrenees.

Moreover, the scale to diagnoses AMS, the Lake Louis Score 2018, has been modified recently to accurate the diagnoses and, to our knowledge, no studies involving AMS have been published using this modified score (22).

Owing to all mentioned before, we can understand the relevance of this project.

## 5 Hypothesis

Acute Mountain Sickness can appear in altitudes higher than 2,500m and based on the revised bibliography and the daily clinical experience by professionals' mountaineers and rescue workers, our main hypothesis is:

1. There is AMS in the Pyrenees and its prevalence must be between 10-30% of mountaineers who climb to heights greater than 2,500m. The grade of AMS will be mild to moderate.

Our secondary hypothesis is:

2. There are differences in the risk factors between the people affected by AMS.

## **6 Objective**

### **6.1 Main Objective**

To determinate the prevalence of AMS in climbers exposed to moderate elevation between 2,500m to 3,404m in the Pyrenees using the Lack Louis Score 2018.

### **6.2 Secondary Objectives**

- To determinate the risk factors related with the development occurrence of AMS.
- To improve knowledge of the AMS by professionals and climbers by the elaboration of an informational brochure about AMS and remind mountaineers of the basics to prevention.

## **7 Methodology**

### **7.1 Study Design**

This is an observational cross-sectional study to determine prevalence.

### **7.2 Study Population**

The study population includes mountaineers who have climbed a mountain with a height greater than 2,500m in the area of the Pyrenees between July and August 2019.

### **7.3 Subjects selection**

#### **7.3.1 Inclusion criteria**

- Mountaineers who voluntarily participated in the study and answered the questionnaire.
- Individuals who have climbed a mountain greater than 2,500m in the Pyrenees area between July and August 2019.

#### **7.3.2 Exclusion criteria**

- Not giving their consent to participate in the study
- Answering the questionnaire inappropriately
- Individuals who have climbed a mountain in another area than the Pyrenees.
- Individuals who have climbed to heights greater than 3,404m (because it is not possible to climb these heights in the Pyrenees)
- Individuals who have climbed to heights less than 2,500m.

## **7.4 Sampling**

### **7.4.1 Sample size**

In order to calculate our sample size, we used the GRANMO Calculator, according to the data of the Annals of Internal Medicine (1993) and BMJ open (2017) (12,15).

A sample size of 400-500 subjects will suffice to estimate with a 95% confidence and a precision  $\pm 4$  per cent units, a population percentage considered to be around 25-30%. It has been anticipated a replacement rate of 10%.

## **7.5 Sample collection**

A non-probabilistic convenience sampling has been performed.

### **7.5.1 Justification of the place**

We have chosen the Pyrenees area because it is the area of the Peninsula where most of the highest mountains are located and the prevalence of mountaineers is rising. One study in Aneto shows the relationship between oxygen saturation and altitude with acclimatization. At the top of Aneto (3,404m), there is an oxygen availability of 62% and a saturation of 84.4% on the first day, and 90.9% on the second day after the acclimation (26).

Related to what we have discussed above, there is a risk of AMS in the Pyrenees, but so far, no studies have determined the prevalence in this area. There is a mountain security campaign (Montaña Segura and Aneto Seguro), which reports on the risks in the mountains, one of them AMS.

### **7.5.2 Types of data collection**

The data collection is divided into two different groups according to the source of the data:

#### **In person**

It has been performed in the Renclusa refuge, in the Posets-Maladeta Nature Reserve in Spain, where most people who climb mountains over 3,000m high, like the summit Aneto or Maladeta, pass. Specifically, in Besurta. This is an area of passage for mountaineers who return of their activity in the mountains or wait for the bus to transfer to the parking car. We have asked them if they want to participate in the study by answering the questionnaire.

During the period of two days (weekend 3<sup>rd</sup> and 4<sup>th</sup> of August 2019), we were interviewing the mountaineers in person in this area.

### **On-line**

The questionnaire could be answered online through a link or QR code once the activity in the mountain was finished (Annex 7. Link and QR code). Allowing to answer it in a quiet place and once resolved AMS.

It has been done with the help of different closed groups related to the Pyrenees and the area studied:

- Montaña Segura and Aneto Seguro: a campaign for the prevention of accidents in the natural environment as a result of a collaboration agreement between the Government of Aragon, Aramón and the Aragonese Mountaineering Federation. Among the activities they carry out, one of them is to interview the people who ascend to the Aneto to assess the profile of people and future prevention.
- Refugio la Renclusa: the mountain refuge located 2,165m high in the area studied.
- Mountain guides in the area and mountain groups that had a scheduled excursion in the area
- Social Media: Amigos de los Pirineos (Facebook group), 3.000 dels Pirineus (Instagram group)

### **7.5.3 Time of recruitment**

The time of recruitment for assessing the sample proposed (450 persons) was approximately two months (July and August 2019). The work done in person has been made for two days, the weekend of 3<sup>rd</sup> and 4<sup>th</sup> of August 2019. The questionnaire online has been opened during this period of two month (July-August)

## 7.6 Measure instruments

To collect all data, a questionnaire has been specially designed for this study. (See Annex 6. Questionnaire Acute Mountain Sickness). The survey proposed it is a simple, brief and easy understandable instrument which occupies a single page. The estimated time to answer the questionnaire is about 3 minutes and no personal data is collected to ensure data protection. It has been printed so that it can be filled in the field work, either by self-administrated.

The questionnaire has been designed to answer it online, using a link <https://bit.ly/maldealtura> and QR code.

### 7.6.1 Questionnaire design

We have reviewed the medical literature on AMS to determinate all the necessary variables in the questionnaire to carry out our study.

It has been sent to a group of experts on the subject by email like Dr. Subirats, Dr. Ayala and Dr. Trullàs. They have reviewed and evaluated the questionnaire.

The language chosen for the online questionnaire as well as written has been Spanish, because it is the language most spoken in the area of the Pyrenees. It has also been possible to translate to Catalan and French in an oral way.

The questionnaire has been designed on a two-sided sheet to be able to easily and simply collect the variables. It has been divided into three paragraphs or sections.

The on-line form, it has been done through the Google Forms program. It is a simple, freeway, and it has allowed us to design the three sections and collect the data without having to collect personal data. We have created a link to disseminate it. This link has been modified with the bit.ly program to abbreviate and thus make diffusion easier.

It consists of 28 questions in total. The three sections are:

1. **First Section:** related to medical history
  - a. Age, Sex, Height and Weight
  - b. Place of residence and sea level situation
  - c. Diseases, medications and analgesics the last 48hours.



- d. Smoking habits
  - e. Physical activity par week and physical condition
  - f. Recent activity at more than 2,500m, night in refuge or at height
  - g. History of HAI
2. **Second section:** characteristics of the current activity
    - a. Reached altitude, time of ascension and unevenness
    - b. Physical exertion and Sporting discipline
    - c. Liters drunk, food and sunscreen
  3. **Third section:** Lake Louise Score for the diagnosis of AMS.

The second page was for comments and informed consent about the work and the use of the data for the study.

### **7.7 Data Collection**

All data has been collected prospectively using the survey with the aim to collect data about AMS in the Pyrenees.

By completing the questionnaire, the participant accepts the informed consent. Participants have been informed of the study, the objectives they intend to achieve and what it will consist of. They have also received a link/tryptic with more information about High-Altitudes Disease once completed the questionnaire. See Annex 8. Tryptic information AMS.

The data, that has been collected online, was gathered in a Google Form, and the privacy and the safety of this form has been ensured.

Once the data collection was concluded, all the data were exported to the statistical software SPSS for analysis.

### **7.8 Variables**

Our study is designed as a cross-sectional one, bringing forth the impossibility to define one single independent variable, as every epidemiological aspect we may want to study will be considered as one. Therefore, we will define these aspects in the way of covariates. A total of 23 variates has been collected.

The variables are classified in four areas. Summarized in Table 3.

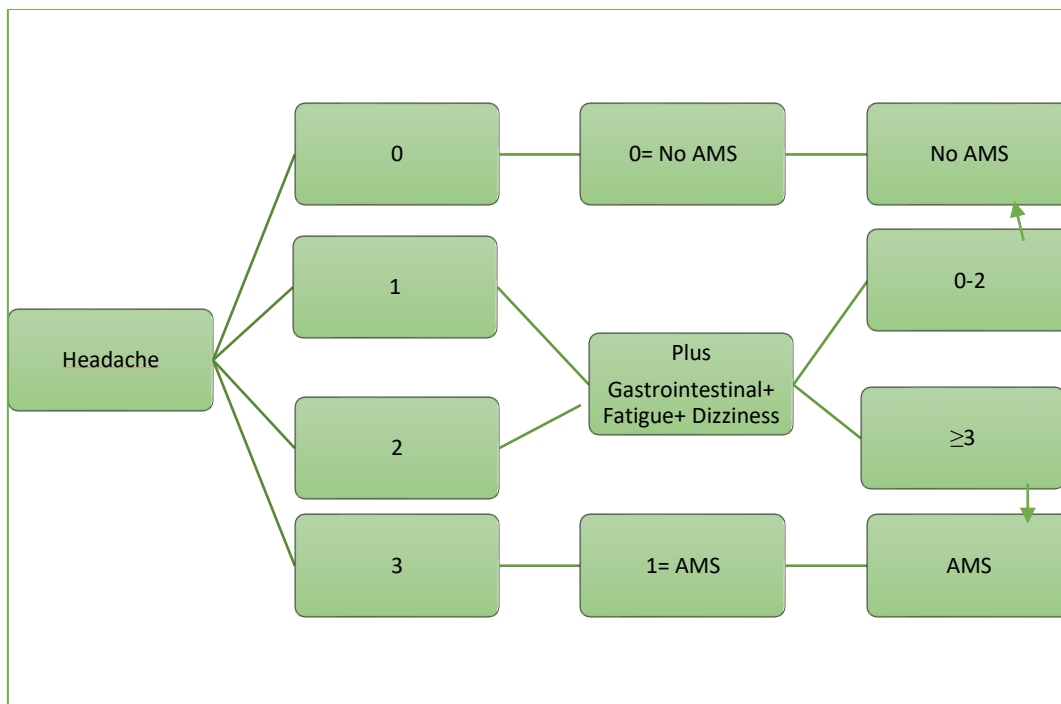
1. **Outcome variable:** Clinical symptoms that developed at altitude using the LLS, indicates the presence or absence of AMS.
2. **Demographic** (age, gender, place of residence)
3. **Medical history** (Body Mass Index [BMI], comorbidities, smoking habits, prior HAI history...)
4. **Activity information** (maximum altitude reached, daily average ascent, time from arrival at altitude...)

### 7.8.1 Main objective. Outcome variable

Our variable of interest, or outcome variable, is the **development of AMS** in the Pyrenees, which was defined according to the LLS criteria 2018, which is the gold standard for diagnoses.

The LLS includes five questions about four different AMS-related symptoms: headache, nausea/vomiting, fatigue and dizziness. The LLS criteria state that an individual is suffering from AMS if the total score is three or more points, including at least one point from headache. Figure 2. AMS Diagnoses.

*Figure 2. AMS Diagnoses.*



## Dependent Variable

Presence (or not) of AMS

### 7.8.2 Secondary objectives: Covariates

As mentioned before, we are managing three groups of covariates:

#### 1. Related to demographical information

- a. Age (continuous quantitative variable): as expressed in years
- b. Gender (dichotomous nominal qualitative variable): analyzed as a closed answer with two options male or female.
- c. Place of residence (qualitative variable): variable collected to know if the place of residence is less than 800m from the sea level, related to the following variable.
- d. Residence located less than 800 m from the sea level (qualitative variable): measured as YES/NO

#### 2. Medical history:

- a. Weight (continuous quantitative variable): expressed in kilograms.
- b. Height (continuous quantitative variable): expressed in meters.
- c. BMI (continuous quantitative variable): expressed in  $\text{kg/m}^2$ . It is calculated through weight (kg) and height ( $\text{m}^2$ ). According to the BMI classification of World Health Organization (WHO) we categorized as
  - i.  $<18.5$  Underweight
  - ii.  $18.5-24.9$  Normal weight
  - iii.  $\geq 25$  Overweight
  - iv.  $\geq 30$  Obese
- d. Comorbidities (dichotomous nominal qualitative variable): measured as YES/NO of the following diseases: Diabetes, Cholesterol, Hypertension, Chronic obstructive pulmonary disease (COPD), Obstructive Sleep Apnea Syndrome (OSAS), Cardiovascular disease, Asthma, Migraine, Anemia. Others
- e. Drugs or natural remedies (dichotomous nominal qualitative variable): measured as YES/NO
- f. Analgesics the last 48h (dichotomous nominal qualitative variable): measured as YES/NO

- g. Smoking (dichotomous nominal qualitative variable): analyzed as a nominal qualitative variable, in terms of non-smoker, smoker and ex-smoker.
- h. Previous HAI (dichotomous nominal qualitative variable): measured as YES/NO
- i. Physical activity per week (dichotomous nominal quantitative variable): measured in hours.
- j. Physical condition (qualitative variable): measured in four options Bad/ Acceptable/ Good/ Very Good

**3. Activity information:**

- a. Higher height reached (quantitative variable): measured in meters
- b. Ascension time (quantitative variable): measured in hours
- c. Accumulated drop (quantitative variable): measured in meters
- d. Rate of ascend (quantitative variable): calculated with accumulate drop and ascension time in meters/hours
- e. Feeling of physical exertion (qualitative variable): categorized as normal, moderate, severe.
- f. Sport or discipline (qualitative variable): categorized as climbing, running, alpinism, others.
- g. Night in a mountain refuge or a height over than 2,500m (qualitative variable): measured as YES/NO
- h. Recent activity above 2,500 before (qualitative variable): measured as YES/NO

*Table 3. Summary of the variables analyzed.*

	<b>Variable</b>	<b>Type</b>	<b>Values</b>
<b>Outcome Variable</b>	Presence AMS	Nominal dichotomous qualitative	Yes/No

	Variable	Type	Values
<b>Demographic</b>	Age	Continuous quantitative	years
	Gender	Nominal dichotomous qualitative	Male / Female
	Place of residence	Nominal qualitative	Name
	Residence <800m sea level	Nominal dichotomous qualitative	Yes/No
<b>Medical History</b>	Weight	Continuous quantitative	Kg
	Height	Continuous quantitative	meters
	BMI	Continuous quantitative	<18.5 18.5-24.9 >15 ≥30
	Comorbidities	Nominal dichotomous qualitative	Yes/ No
	Drugs/ Natural remedies	Nominal dichotomous qualitative	Yes/No
	Analgesics	Nominal dichotomous qualitative	Yes/ No
	Smoking status	Ordinal qualitative	Non-smoker Smoker Ex-smoker
	History of AMS	Nominal dichotomous qualitative	Yes/ No
	Physical activity week	Continuous quantitative	Hours/week
Physical condition	Ordinal qualitative	Bad Acceptable Good Very Good	
<b>Activity information</b>	Higher height	Continuous quantitative	meters
	Ascension time	Continuous quantitative	hours
	Accumulated drop	Continuous quantitative	meters
	Rate of ascend	Continuous quantitative	Meters/hours
	Intensity effort	Ordinal qualitative	Normal Moderate Intense
	Sport discipline	Nominal qualitative	Running Alpinism Climbing
	Night in height	Nominal dichotomous qualitative	Yes/ No
	Recent activity >2,500m	Nominal dichotomous qualitative	Yes/No

## **8 Statistical Analysis**

### **8.1 Descriptive analysis**

Due to the characteristics of a cross-sectional study, we cannot define our variables in terms of dependent and independent. However, we consider the presence of AMS as the outcome variable (qualitative variable), and we study its occurrence in relation to a group of covariates. For qualitative or categorical variables, results have been expressed as percentages and number of patients. For quantitative variables, assuming that they are not normally distributed, are summarized as median and interquartile range [IQR]. We also computed the means, standard deviation for the presence or absence of AMS.

The association between the outcome variable and for categorical variables are summarized in a contingency table.

### **8.2 Bivariate analyses**

A Chi-square test ( $\chi^2$ ) has been used to assess the relationship between our variable interest, presence of AMS, and the qualitative variables. When the expected number of cases in any of the cells was lower than 5, the Fisher exact test was used. The Kolmogorov–Smirnov test was used to determine whether quantitative variables were normally distributed. For the analysis of the relationships between the presence of AMS and quantitative variables, a Mann-Whitney test has been used for the non-normally distributed ones. For normally distributed variables, a Student's T test has been performed.

### **8.3 Multivariate analyses.**

A logistic regression analysis has been performed to assess the association between both groups of patients (those with AMS) and the covariates. The analysis has been adjusted for covariates that are statistically significant ( $p < 0.05$ ) in the analysis bivariate and those risk/protective factors who are related with AMS in literature.

Statistical significance was set at 0.05. Analyses were performed with the software Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS, Inc., Chicago, Illinois, USA).

## 9 Working plan

The study has been performed in one year and it has been composed of 4 phases with different objectives and activities in each part. A chronogram is presented on the next page for easy visualization of the whole process.

- **Phase 1: Preparation and coordination:** (November 2018- May 2019)
  - Study design with exhaustive bibliographic research and protocol elaboration.
  - Questionnaire elaboration with the help of different professional's experts in the field such as Dr. Subirats, Dr. Ayala, Dr. Trullàs. Informative triptych elaboration with the main symptoms and prevention measures.
  - Contact with security mountain campaigns, Renclusa refuge, professionals rescue workers, mountain groups...
- **Phase 2 Data collection** (July- August 2019)
  - From July to August 2019 the recruitment of climbers has been performed, in the high season of climbers ascending the Aneto.
  - Open the questionnaire online
  - Take the survey in person in Besurta during the weekend 3<sup>rd</sup> and 4<sup>th</sup> of August. And with the help of Montaña Segura, Mountain Guides, La Renclusa refugee, Social Media...with an online questionnaire.
  - Development of a database with the SPSS program
  - Run the data through the SPSS program
- **Phase 3: Data analysis and final evaluation** (September 2019)
  - Dr. Trullàs has performed the statistical analysis and we meted twice for results discussion and interpretation. Also, Prof. Saez has contributed.
- **Phase 4: Publication and dissemination of the results** (February 2020)
  - The results will be presented in
    - Montaña Segura and Aneto Seguro, FEDME
    - Submitted to publish in a wilderness medicine journal such as Wilderness & Environmental Medicine Journal or High-Altitude Medicine & Biology
    - Diffusion on ski resorts, mountain groups, social networks

	Nov 19	Dec 19	Jan 19	Feb 19	Mar 19	Apr 19	Ma 19	Jun 19	Jul 19	Aug 19	Sept 19	Oct 19	Nov 19	Des 19	Jan 20	Feb 20	Mar 20		
<b>Phase 1</b> Preparation and coordination	Bibliographic research, study design and protocol elaboration																		
		Questionnaire and triptych elaboration																	
		Contact with Aneto y Montaña Segura, La Renclusa, professionals rescue workers...																	
<b>Phase 2</b> Data collection	Open the questionnaire online																		
	Take the survey in person and with the help of Montaña Segura, mountain guides...																		
	Development of database SPSS																		
<b>Phase 3</b> Data analysis and final evaluation	Run the data through SPSS																		
	Data analysis and final evaluation with Dr. Trullàs																		
<b>Phase 4</b> Publication and dissemination of the results	Present the results to Montaña Segura. Submitted to publish in a wilderness medicine journal. Diffusion ski resorts, mountain groups and social media																		



## **10 Ethical Aspects**

The works has always been done by previously informing the people that voluntary participated in the completion of the questionnaire. They have been informed of the study, the objectives they intend to achieve and what it will consist of. By completing the questionnaire, the participant accepts the informed consent.

To maintain the confidentiality and data security, no personal data was collected, no names, postcodes, addresses, birth dates or other numbers are collected. The security of data has been ensured on locked network which only be accessible for the principal responsible researchers of the project.

According to the national and international laws regarding autonomy, the study is governed by “Organic Law 15-1999 of December 13th, of protection of personal data. So, the exposed results do not allow in whole part the identification of any involved in the sample studied.

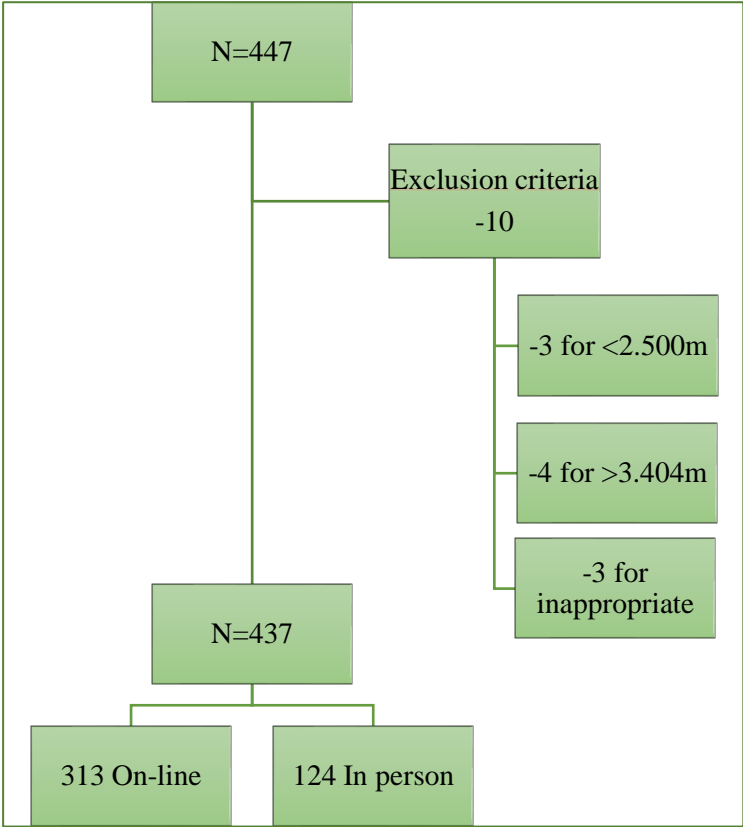
It hasn't existed either in the present study no external financing or conflict of interests.

# 11 Results

## 11.1 Baseline Characteristics

During the period of two month, 447 participants were registered. After discarding 10 people following the exclusion criteria, the resulting sample size was 437 individuals. 323 were obtained On-line, and 124 in person. Figure 3. Flow of participants in the study

Figure 3. Flow of participants in the study



## Demographical information

Four hundred and thirty-seven individuals were included in the study, 71.4% were males and the mean age was 35 years. The major part of the sample lives in a residence below 800m (89.9%). See Table 4.

*Table 4. Demographic characteristics*

Variable		Results
Male Gender n (%)		314 (71.4)
Age (years)	mean (SD)	35 (11.8)
	median [IQR]	34 [18]
Residence below 800m n (%)		393 (89.9)

## Medical History

The results of anthropometric measurements show that most of the participants were within normal BMI values, with BMI mean of 22.9 kg/m<sup>2</sup> as we can see in Table 5.

*Table 5. Medical characteristics (Weight, Height, BMI)*

Variable		Results
Weight (kg)	mean (SD)	69 (11.5)
	median [IQR]	70 [14]
Height (m)	mean (SD)	1.7 (0.9)
	median [IQR]	1.7 [0.12]
BMI	mean (SD)	22.9 (2.6)
	median [IQR]	22.8 [3.2]
BMI category n (%)	Low weight	13 (3)
	Normal	348 (79.6)
	Overweight	69 (15.8)
	Obesity	7 (1.6)

In the Table 6, we can see that 80% of individuals did not present any comorbidity. Cholesterol was the most frequent comorbidity (3.7%). Related to the use of analgesics, 60 (13.7%) participants use some painkiller. Most of the participant were no smokers (70.3%). A 10.3% of the participants were smokers, and 19.5% former smokers.

The Table 6 also shows that, the previous history of HAI was found in 105 mountaineers (24%). The mean values of physical activity were 8 hours/week. The physical condition subjectively assessed shows that 61.3% had a good physical condition.

*Table 6. Medical characteristics (others)*

	<b>Variable</b>	<b>Results (n%)</b>
Comorbidities	Diabetes	1 (0.2)
	Cholesterol	16 (3.7)
	Hypertension	11 (2.5)
	OSAS	6 (1.4)
	COPD	0
	Cardiovascular	3 (0.7)
	Asthma	12 (2.7)
	Migraine	7 (1.6)
	Anemia	8 (1.8)
	Hypothyroidism	6 (1.4)
	Other	15 (3.4)
Drugs	Yes	47 (10.8)
Natural	Yes	11 (2.5)
Analgesics	Yes	60 (13.7)
Smoking habits	No Smoker	307 (70.3)
	Former smoker	85 (19.5)
	Smoker	45 (10.3)
HAI history n (%)	Yes	105 (24)
Physical activity (h/week)	mean (SD)	8 (5)
	median [IQR]	7 [5]
Physical condition n (%)	Bad	6 (1.4)
	Acceptable	82 (18.8)
	Good	268 (61.3)
	Very good	81 (18.5)

**Activity Information**

As we can see in Table 7, 148 (33.9%) of the participants had done a recent activity at more than 2,500m high and only 116 (26.5%) slept in a mountain refuge or in height. The mean altitude is 3,277 m and the range are from 2,500 to 3,404 m (related to the inclusion/exclusion criteria). The mean time is 5 hours.

Most of the participants, 237 (54.2%), had a feeling of moderate exercise exertion; 101 (23.1%) intense and 99 (22.7%) normal. Mountaineering was the most practiced sports discipline with a total of 284 (65%) participants, followed by alpinism 102 (23.3%) and running 48 (11%).

*Table 7. Activity Characteristics*

Variable		Results n (%)
Recent activity >2,500m	Yes	148 (33.9)
Sleep or Refugee >2,500m	Yes	116 (26.5)
Altitude (m)	mean (SD)	3277 (201)
	median [IQR]	3404 [263]
Time (h)	mean (SD)	5.3 (1.8)
	median [IQR]	5 [9]
Unevenness (m)	mean (SD)	1537 (430)
	median [IQR]	1500 [300]
Ascension rate (m/h)	mean (SD)	317 (140)
	median [IQR]	300 [110]
Physical exertion	Normal	99 (22.7)
	Moderate	237 (54.2)
	Intense	101 (23.1)
Discipline	Mountaineering	284 (65)
	Running	48 (11)
	Alpinism	102 (23.3)

## 11.2 Prevalence of AMS

AMS was presented in 117 participants while 320 did not meet the criteria for AMS. The prevalence of AMS is 26.6% with an 95% confidence interval between 22.7% and 30.9%.

The prevalence of AMS in the respondents online was 26.6% and on paper 29.9%. The difference did not reach statistical significance.

Related to the severity of the symptoms, as we can see in Table 8, of the 117 participants who presented AMS, 103 (88%) had mild symptoms, 14 (12%) moderate and fortunately no one suffered a serious case.

*Table 8. Severity of AMS*

	Frequency (n)	Percentage (%)
<b>Mild</b>	103	88
<b>Moderate</b>	14	12
<b>Severe</b>	0	0

As we can see in Table 9, fatigue was present in 98.3% of cases of AMS, being the most frequent symptom (apart from headache, which is a mandatory criterion for diagnosis). Moreover, also was the one with more severe affection (8.5%).

The next most frequent symptom were the gastrointestinal ones (59%) and ultimately dizziness (47%).

*Table 9. Severity of the symptoms*

	0 Not at all	1 Mild	2 Moderate	3 Severe	Total n (%)
<b>Headache</b>	0	88 (75.2)	25 (21.4)	4 (3.4)	117 (100)
<b>Gastrointestinal</b>	48 (41)	65 (55.6)	3 (2.6)	1 (0.9)	69 (59)
<b>Fatigue</b>	2 (1.7)	57 (48.7)	48 (41)	10 (8.5)	115 (98.3)
<b>Dizziness</b>	62 (53)	45 (38.5)	9 (7.7)	1 (0.9)	55 (47)

### 11.3 Risk factors for AMS (analysis bivariant)

#### **Demographical information**

Women report a major risk of suffering AMS, but we not found statistic differences. Residence below 800m was aside of the statistical significance, being a potential risk factor. Table 10.

*Table 10. Demographical association with AMS*

	<b>AMS NO</b> <b>N=320</b>	<b>AMS Yes</b> <b>N=117</b>	<b>p value</b>
<b>Male n (%)</b>	236 (73.8)	76 (65.0)	0.072
<b>Age (years)</b>	34 [17]	33 [19]	0.704
<b>Residence&lt;800m n (%)</b>	283 (88.4)	110 (94.0)	0.086

#### **Medical History**

As we can see in Table 11, no significant difference was found in anthropometric data (weight, size and BMI). Of the comorbidities analyzed, it should be noted that the only one that has had statistical significance (p-value<0.05) has been SOAS, whit 4 participants who have OSAS develop AMS. No significant differences were found with smokers, ex-smokers and AMS.

The use of analgesics, such as NSAIDs, has been statistically related to a higher risk of AMS (p-value 0.013).

The previous history of AMS has been related to a higher risk of developing AMS. Of the total participants who had a history of HAI, 40 (34.2%) have manifested AMS, being statistically significant (p-value 0.003).

Having a bad physical condition and practicing fewer hours of activity during the week has been associated with having higher risk of suffering from AMS.

Table 11. Medical association with AMS

	AMS NO N=320	AMS Yes N=117	p value
<b>Weight (kg)</b>	70 [14]	69 [17]	0.548
<b>Height (m)</b>	1.7 [0.1]	1.7 [0.1]	0.245
<b>BMI (kg/m<sup>2</sup>)</b>	22.8 [3.1]	22.9 [3.4]	0.920
<b>Comorbidities n (%)</b>			
<b>Diabetes</b>	1 (0.3)	0	0.545
<b>Cholesterol</b>	12 (3.8)	4 (3.4)	0.870
<b>Hypertension</b>	7 (2.2)	4 (3.4)	0.467
<b>Cardiovascular</b>	1 (0.3)	2 (1.7)	0.117
<b>Asthma</b>	9 (2.8)	3 (2.6)	0.888
<b>OSAS</b>	2 (0.6)	4 (3.4)	<b>0.026</b>
<b>Migraine</b>	5 (1.6)	2 (1.7)	0.914
<b>Anemia</b>	5 (1.6)	3 (2.6)	0.489
<b>Drug use n (%)</b>	32 (10.0)	15 (12.8)	0.399
<b>Naturals use n (%)</b>	7 (2.2)	4 (3.4)	0.481
<b>Analgesics use n (%)</b>	36 (11.2)	24 (20.5)	<b>0.013</b>
<b>Smoker n (%)</b>	32 (10.0)	13 (11.1)	0.937
<b>History HAI n (%)</b>	65 (20.3)	40 (34.2)	<b>0.003</b>
<b>Hours activity/week</b>	7.5 [5]	6.0 [4.0]	<b>&lt;0.001</b>
<b>Physical condition n (%)</b>			
<b>Bad</b>	4 (1.2)	2 (1.7)	<b>0.019</b>
<b>Acceptable</b>	49 (15.3)	33 (28.2)	
<b>Good</b>	203 (63.4)	65 (55.6)	
<b>Very Good</b>	64 (20.0)	17 (14.5)	

### Activity Information

In terms of activity realized, are shown in Table 12. Participants affected from AMS reported higher times of ascension [2.0] than people not affected (p-value <0.05). The accumulated drop was aside of the statistical significance, being a major risk to suffer AMS those who performed a higher accumulated slope.



The intensity of the physical exertion has been related to the development of AMS. Those whose physical effort was intense, developed more AMS and were significantly more frequent than participants without AMS (p-value <0.05).

No relationship was found with the development of AMS and the sport modality practiced.

Of the participants who performed a recent activity at a height greater than 2,500m, 116 (36.2%) did not develop AMS and 32 (27.4%) did. Concluding that it could be a protective factor, but it did not obtain statistical significance.

*Table 12. Activity association with AMS*

	<b>AMS NO</b> <b>N=320</b>	<b>AMS Yes</b> <b>N=117</b>	<b>p value</b>
<b>Altitude (m)</b>	3404 [294]	3404 [260]	0.101
<b>Ascension time (h)</b>	5.0 [1.0]	5.0 [2.0]	<b>0.032</b>
<b>Unevenness (m)</b>	1500 [313]	1500 [290]	0.079
<b>Ascension rate (m/h)</b>	320 [95]	316 [108]	0.540
<b>Physical exertion n (%)</b>			
<b>Normal</b>	84 (26.2)	15 (12.8)	
<b>Moderate</b>	183 (57.2)	54 (46.2)	
<b>Intense</b>	53 (16.6)	48 (41.0)	<b>&lt;0.001</b>
<b>Discipline n (%)</b>			0.742
<b>Mountaineering</b>	206 (64.4)	78 (66.7)	
<b>Running</b>	36 (11.2)	12 (10.3)	
<b>Alpinism</b>	75 (23.4)	27 (23.1)	
<b>Recent activity &gt;2,500</b>	116 (36.2)	32 (27.4)	0.082
<b>Night in the refugee</b>	83 (25.9)	33 (28.2)	0.635

### 11.4 Multivariate Analysis

The adjusted odds ratio for the prevalence of AMS regarding the significant risk factors are shown in Table 13 and summarized in Figure 4 regarding the most relevant factors.

The risk of suffering AMS was 95% higher when participants took some type of analgesic (such as NSAIDs) than who not (aOR 1.95, 95% CI 1.09 to 3.50). A history of HAI enhanced the risk for AMS by 1.98 (1.22 to 3.21) times. Participants who has a good physical condition effected a risk reduction of 0.48 (0.29 to 0.79) to develop AMS.

The most significant risk factor was heavy exertion during the ascent, leading to a 2.24 (1.22 to 4.12) fold higher risk compared to those who did had no lassitude.

*Figure 4. Adjusted Odds Ratio for AMS (95% CI) regarding the most relevant factors*



Table 13. Results of multiple logistic regression for predictors of AMS

	<b>Unadjusted OR (CI 95%)</b>	<b>p value</b>	<b>Adjusted OR (CI 95%)</b>	<b>p value</b>
<b>Age</b>	0.99 (0.98-1.01)	0.62	0.98 (0.96-1.0)	<i>0.091</i>
<b>Male gender</b>	0.65 (0.42-1.04)	0.072	0.62 (0.36-1.06)	<i>0.081</i>
<b>Residence &lt;800</b>	2.06 (0.89-4.75)	0.086	1.75 (0.72-4.26)	0.220
<b>BMI</b>	1.01 (0.95-1.09)	0.74	1.04 (0.93-1.16)	0.477
<b>OSAS</b>	5.63 (1.02-31.4)	0.026	3.54 (0.52-24.2)	0.197
<b>Analgesics</b>	2.04 (1.16-3.56)	0.013	1.95 (1.09-3.50)	<b>0.026</b>
<b>Smoke</b>	1.07 (0.67-1.69)	0.78	1.037 (0.62-1.73)	0.889
<b>History HAI</b>	2.04 (1.23-3.26)	0.003	1.98 (1.22-3.21)	<b>0.006</b>
<b>Physical activity (h/week)</b>	0.92 (0.82-0.98)	0.004	0.94 (0.89-1.00)	<i>0.062</i>
<b>Good physical condition</b>	0.47 (0.28-0.76)	0.002	0.48 (0.29-0.79)	<b>0.004</b>
<b>Altitude</b>	1 (1.0-1.0)	0,25	1.0 (0.99-1.0)	0.327
<b>Ascension time</b>	1.19 (0.99-1.44)	0.063	1.06 (0.82-1.36)	0.672
<b>Unevenness</b>	1 (1.0-1.0)	0.15	1.0 (0.99-1.0)	0.603
<b>Physical exertion</b>	2.42 (1.33-4.40)	0.003	2.24 (1.22-4.12)	<b>0.009</b>
<b>Activity &gt;2,500m</b>	0.66 (0.42-1.06)	0.082	0.69 (0.42-1.14)	0.150

## **12 Discussion**

### ***Prevalence of AMS***

To our knowledge, this is the first study that analyzes the prevalence and risk factors of altitude sickness in the Pyrenees.

One hundred seventeen of 437 mountaineers (26.2%) ascending to moderate to high altitudes in the Pyrenees developed AMS, when defined as the presence of headache and a LLS  $\geq 3$ . We consider that it is a quite high prevalence in relation to poor knowledge of this pathology in the area.

No studies have assessed the prevalence of AMS in the Pyrenees. Although it is difficult to compare these results directly with previous studies, owing to the geographic locations and different populations that were studied, the prevalence of AMS on the Pyrenees seemed to overlap with previous studies at similar height (2,500 to 3,404m). Prevalence of about 25% at altitudes between 1,900 and 2,950 m in the Rocky Mountains Colorado (12), 29.5% at 3,776m in Mt Fuji (8), 38.0% at 3,454m in the Eastern Alps and 34.9% at 3,817m in the Western Alps (27).

### ***Risk factors for AMS***

The level of exertion subjectively assessed has shown to be an independent risk factor for AMS those who report heavy exertion. These findings can be explained due to the stress caused in the autonomic nervous system by additional hypoxia that generates an intense exercise. Same risk factor has been reported in other studies (3) (11).

The odds ratio of suffering AMS was doubled for mountaineers who had a history of altitude illness on previous exposures. Based on our findings and those of previous researchers, a strong relationship seems to exist between a self-report of previous HAI and the risk of subsequent development of AMS (4,6,10,12,28).

Moreover, self-assessed bad physical condition has proved to be a significant risk factor for the development of AMS. This can be explained in part by the fact that the physical condition is related to the level of exertion during the ascent, suggesting that low fitness climbers do not tolerate the unusual exertion of mountaineering, or they appear to workout excessively. These results support some studies carried out (12,27), while other studies conclude that the physical condition does not protect against AMS (10,28).

However, in the development of AMS, self-reported hours of training per week was borderline to be a significant statistical factor. This can be explained because self-report data is a difficult parameter to evaluate, as there may be considerable variability in “training” and “physical activity” inter-individual interpretation.

The final variable with a significant relationship to AMS was the ingestion of analgesics, which included NSAIDs (ibuprofen, naproxen...), acetylsalicylic acid, or acetaminophen. This findings can generate confusion and deserves to be clarified: this finding is the result of trekkers with AMS taking analgesics to relieve their symptoms instead of analgesics "causing" them (28). The relationship of the use of analgesics with AMS is not established, some studies show efficacy as prevention (29,30). The Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update (17), recommend the use of Ibuprofen (grade 1C to treat headache at high altitude, 2B for prevention in AMS in persons who do not wish to take acetazolamide or dexamethasone or have allergies or intolerances to these medications) and acetaminophen (grade 1C to treat headache, but not recommended for AMS prevention)

It is commonly accepted that residing at an altitude above 800m of the sea level offers some protection against AMS (12,19); however, our sample probably did not have enough participants living at moderates altitudes to test this hypothesis accurately. Only 10.1% of the sample lived above 800m, and this may not have been a high enough altitude to offer a protective effect.

The same effect could be happened by preexposure at altitudes above 2,500m which offers some protective benefit against AMS (10,17). Our data do not confirm this association, with only 33.9% has done a preexposure to altitudes above 2,500m.

Therefore, subjects who suffered from AMS once may prepare themselves better by taking precautions, such as adequate acclimatization; less exerting ascent; good physical condition; and pharmacological prevention those with history of HAI. Although it is known that physiological and genetic characteristics predispose people to develop AMS, our results suggest that an appropriate behavior may reduce individual susceptibility.

## 12.1 Limitations

As any study design, there are different limitations that interfere in the proper study performance and their end results.

As an observational study, without a randomization of the subjects in the different categories of the independent variable, it is possible that there are some confounding factors that we have not included as co-variables.

A descriptive study cannot establish causal relationships and therefore the results and conclusions should it be assessed with other types of studies.

This study has used a non-probabilistic sampling method, which means that the subjects of the study population does not have the same chance to be elected to constitute the sample, which could lead to a non-representative sample.

We have used two types of samples, the ones in paper and the ones online. People who had moderate-sever AMS were not able to complete the questionnaire in person, thus losing some serious cases. The alternative has been the online form, where the sample has been more numerous than the sample obtained in person. Owing to the mountaineers were very tired of their excursion or were in a hurry to take the bus or the car. Thus, has allowed that people were able to answer the questionnaire once the activity was finished completely and they were not affected by fatigue or AMS. We compared the prevalence of AMS in both samples and no statistical difference was found.

Non-response is a particular problem affecting cross-sectional studies and can result in bias of the measures of outcome. This is a problem when the characteristics of non-responders differ from responders. In this study we couldn't measure the rate of response, but we think that is approximately 60%.

Using a survey may cause an information bias due to the Hawthorne effect because participants can think that they are being evaluated so they may have changed their decisions. Suffering from AMS may be poorly considered among mountaineers since it is confused with other pathologies or is considered as a weakness, lack of training or that appears in very high altitudes. Therefore, it may be that the results obtained in this study are lower than the real ones.

The data collected were from a self-report questionnaire and interview conducted retrospectively as trekkers completed their descent. We make the assumption that they could accurately recall their ascent data, AMS symptoms, and give truthful answers.

As mentioned, much of the sample has been obtained online and there is a possibility that the sources obtained are not reliable. We have tried to avoid this bias by reviewing the responses and discarding those that were inappropriate or incongruous. Comparing with the studies carried out in the area, studies with same characteristics and evaluating the statistical difference with the two types of sample; the results are quite similar.

Ascension time is difficult to assess since the total activity time is usually remembered. The sport modality practiced is ambiguous to ask since there are no exact definitions for alpinism, mountaineering, climbing... It would be necessary to assess alcohol intake as possible risk factor or differential diagnosis. The socioeconomic level has not been assessed. The question related to the use of analgesics should have been assessed in relation to the consumption or not for alleviate the symptoms of AMS.

We have used the LLS, the gold standard test to diagnose AMS. Some studies have been made to compare different instruments and they recommend using LLS to assess the severity. Thus, the bias of misclassified is avoided.

The triptych provided aims to change the poor knowledge about AMS and try to avoid future risks in the mountain by identifying the alarm symptoms.

On the other hand, since there is a lack of investigation on this topic, we consider this study could be a breakthrough in terms of what we know right now about AMS in the Pyrenees.

## **13 Conclusions**

In conclusion, the prevalence of AMS in mountaineers at altitudes lower than 3,404m at the Pyrenees is not negligible (26,6%). The individuals who developed AMS had mild (88%) or moderate (12%) symptoms and we did not find any severe case of AMS.

The independent risk factors for developing AMS in these hikers are previous history of HAI and other modifiable risk factors such as physical exertion and bad physical condition.

We believe that more educational/informational programs for individuals planning to climb to moderate-high altitudes in the Pyrenees would contribute to prevent AMS.



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## 17 Annexes

### 17.1 Annex 1. Classification of altitude levels

Table 14. Classification of altitude levels (2)

Altitude level	Remarks
Near sea level (0–500 m)	No altitude-related problems
Low altitude(>500–2000 m)	<ul style="list-style-type: none"> <li>• A mild limitation of aerobic performance capacity is demonstrable, particularly in well-trained individuals</li> <li>• No additional problems in stable patients engaging in the same physical activities as at sea level</li> </ul>
Moderate altitude(>2000–3000 m)	<ul style="list-style-type: none"> <li>• Threshold altitude for acute mountain sickness; usually no danger of HACE or HAPE; acclimatization is important for optimal performance capacity</li> <li>• Generally well tolerated by patients with stable disease and adequate reserve performance capacity; restrict activities over the first few days and ascend slowly above 2000 m; beware of contraindications</li> </ul>
High altitude(>3000–5500 m)	<ul style="list-style-type: none"> <li>• Acclimatization important to prevent altitude sicknesses; marked limitation of performance capacity</li> <li>• 3000–4000 m: even stable patients with good performance capacity need thorough evaluation beforehand</li> <li>• &gt;4000 m: generally inadvisable for patients</li> </ul>
Extreme altitude (>5500 m)	<ul style="list-style-type: none"> <li>• remaining at this altitude leads to progressive physical decline (loss of performance capacity, catabolism)</li> <li>• short stays only for healthy, well-trained persons</li> </ul>

**17.2 Annex 2. Risk of HAI***Table 15. Risk categories for AMS*

<b>Risk of HAI</b>	<b>Description</b>
<b>Low</b>	No prior history of altitude illness and planning ascent to <2.800m
	Individuals taking $\geq 2$ d to arrive at 2500e3000 m with subsequent increases in sleeping elevation <500 m and an extra day for acclimatization every 1000 m
<b>Moderate</b>	Prior history of AMS and ascending to 2.500m to 2.800m in 1d
	No history of AMS and ascending to 2.800m or higher in 1d
	Ascending >500 m/day (increase in sleeping elevation) at altitudes above 3.000m but with an extra day for acclimatization every 1.000m
<b>High</b>	History of severe altitude illness (HACE, HAPE)
	History of AMS and ascending to 2.800 m or higher in 1d
	Ascending over 3.500m in less in 1d
	Ascending >500m/day (increase in sleeping elevation) above 3.000m without extra days for acclimatization;
	Very rapid ascents (eg. Mt Kilimanjaro in <7days)

**17.3 Annex 3. Diagnostic criteria High-altitude headache**

*Table 16. Diagnostic criteria High-Altitude Headache*

A. Headache fulfilling criterion C
B. Ascent to altitude above 2,500 meters has occurred
C. Evidence of causation demonstrated by at least two of the following: <ol style="list-style-type: none"><li>1. either or both of the following:<ol style="list-style-type: none"><li>a) headache has significantly worsened in parallel with continuing ascent</li><li>b) headache has resolved within 24 hours after descent to below 2,500 meters</li></ol></li><li>2. headache has at least two of the following three characteristics:<ol style="list-style-type: none"><li>a) bilateral location</li><li>b) mild or moderate intensity</li><li>c) aggravated by exertion, movement, straining, coughing and/or bending</li></ol></li></ol>
D. Not better accounted for by another diagnosis.



**17.4 Annex 4. Differential Diagnosis of High- Altitude Illnesses**

*Table 17. Differential Diagnosis of HAI*

<b>Acute mountain sickness and High-altitude cerebral edema</b>	<b>High- altitude pulmonary edema</b>
<ul style="list-style-type: none"> <li>- Acute psychosis</li> <li>- Arteriovenous malformation</li> <li>- Brain tumor</li> <li>- Carbon monoxide poisoning</li> <li>- Central nervous system infection</li> <li>- Dehydration</li> <li>- Diabetic ketoacidosis</li> <li>- Exhaustion</li> <li>- Hangover</li> <li>- Hypoglycemia</li> <li>- Hypothermia</li> <li>- Ingestion of toxins, drugs, or alcohol</li> <li>- Migraine</li> <li>- Seizures</li> <li>- Stroke</li> <li>- Transient ischemic attack</li> <li>- Viral or bacterial infection</li> </ul>	<ul style="list-style-type: none"> <li>- Asthma</li> <li>- Bronchitis</li> <li>- Heart failure</li> <li>- Hyperventilation syndrome</li> <li>- Mucus plugging</li> <li>- Myocardial infarction</li> <li>- Pneumonia</li> <li>- Pulmonary embolus</li> </ul>

**17.5 Annex 5. Pharmacologic treatment and prevention of HAI***Table 18. Pharmacologic treatment and prevention of HAI*

<b>Condition</b>		<b>Preferred agent</b>	<b>Alternatives</b>
AMS/HACE	<b>Prevention</b>	<b>Acetazolamide:</b> 125 mg orally every 12 hours	<b>Dexamethasone:</b> 2 mg orally every 6 hours or 4 mg orally every 12 hours
	<b>Treatment mild AMS</b>	<b>Acetazolamide:</b> 125 to 250 mg orally every 12 hours	<b>Dexamethasone:</b> 2 to 4 mg orally every 6 hours
	<b>Treatment moderate to severe AMS</b>	<b>Dexamethasone:</b> 4 mg orally every 6 hours	<b>Acetazolamide:</b> 125 to 250 mg orally every 12 hours
	<b>HACE treatment</b>	<b>Dexamethasone:</b> 8 to 10 mg orally /IM/IV once, then 4 mg orally/IM/IV every 6 hours	<b>Acetazolamide:</b> 250 mg orally every 12 hours, may use as adjunct with dexamethasone; NOT for monotherapy

17.6 Annex 6. Questionnaire Acute Mountain Sickness

## CUESTIONARIO MAL DE ALTURA

¡Buenos días! Soy una estudiante de Medicina y estoy haciendo el Trabajo Final de Grado sobre el Mal de Altura en los Pirineos. Me gustaría que respondiera estas preguntas, serán solo 3 minutos y no se recogen datos personales. Muchas gracias por su tiempo.

<b>Edad:</b> _____	<b>Sexo:</b> <input type="checkbox"/> Mujer <input type="checkbox"/> Hombre	<b>Altura (metros):</b> _____ <b>Peso (kg):</b> _____												
<b>Lugar de Residencia:</b> _____		<b>¿Reside en un lugar situado a menos de 800m de desnivel del mar?</b> <input type="checkbox"/> NO <input type="checkbox"/> SI												
Marque con un X si presenta alguna <b>enfermedad</b> como: <table style="width: 100%; border: none;"> <tr> <td><input type="checkbox"/> Diabetes</td> <td><input type="checkbox"/> Hipertensión</td> <td><input type="checkbox"/> Enfermedad cardiovascular</td> <td><input type="checkbox"/> Asma</td> </tr> <tr> <td><input type="checkbox"/> Colesterol</td> <td><input type="checkbox"/> Apnea obstructiva del sueño</td> <td><input type="checkbox"/> Enfermedad pulmonar, EPOC</td> <td><input type="checkbox"/> Migraña</td> </tr> <tr> <td></td> <td></td> <td></td> <td><input type="checkbox"/> Anemia</td> </tr> </table>			<input type="checkbox"/> Diabetes	<input type="checkbox"/> Hipertensión	<input type="checkbox"/> Enfermedad cardiovascular	<input type="checkbox"/> Asma	<input type="checkbox"/> Colesterol	<input type="checkbox"/> Apnea obstructiva del sueño	<input type="checkbox"/> Enfermedad pulmonar, EPOC	<input type="checkbox"/> Migraña				<input type="checkbox"/> Anemia
<input type="checkbox"/> Diabetes	<input type="checkbox"/> Hipertensión	<input type="checkbox"/> Enfermedad cardiovascular	<input type="checkbox"/> Asma											
<input type="checkbox"/> Colesterol	<input type="checkbox"/> Apnea obstructiva del sueño	<input type="checkbox"/> Enfermedad pulmonar, EPOC	<input type="checkbox"/> Migraña											
			<input type="checkbox"/> Anemia											
<b>¿Toma medicación y/o remedios naturales?</b> <input type="checkbox"/> NO <input type="checkbox"/> SI <b>¿Cuál/es?</b> _____														
<b>¿Ha tomado algún antiinflamatorio o analgésico (ibuprofeno, naproxeno, paracetamol...) las últimas 48h?</b> <input type="checkbox"/> NO <input type="checkbox"/> SI														
<b>¿Fuma o es exfumador?</b> <input type="checkbox"/> NO <input type="checkbox"/> SI <b>¿Cuántos cigarrillos/día?</b> _____														
<b>¿Cuántas horas de actividad física practica durante la semana?</b> _____	<b>¿Cómo califica su condición física general?</b> <input type="checkbox"/> Mala <input type="checkbox"/> Aceptable <input type="checkbox"/> Buena <input type="checkbox"/> Muy buena													
<b>¿Ha realizado una actividad a &gt;2.500m recientemente?</b> <input type="checkbox"/> NO <input type="checkbox"/> SI		<b>¿Ha dormido la noche previa en el refugio?</b> <input type="checkbox"/> NO <input type="checkbox"/> SI												
<b>¿Ha presentado mal de altura anteriormente? (dolor de cabeza, edema cerebral, edema pulmonar)</b> <input type="checkbox"/> NO <input type="checkbox"/> SI														

**Durante la actividad actual:** Nota: si ha subido al Aneto altitud 3.404m; desnivel 1.500m

<b>Mayor altitud conseguida</b> _____	<b>Tiempo aprox. ascensión</b> _____	<b>Desnivel acumulado</b> _____	<b>Sensación intensidad del esfuerzo</b> <input type="checkbox"/> Normal <input type="checkbox"/> Moderado <input type="checkbox"/> Intenso
<b>¿Qué deporte ha practicado?</b> <input type="checkbox"/> Alta montaña/montañismo <input type="checkbox"/> Trail-running <input type="checkbox"/> Alpinismo/ crestas			
<b>¿Cuántos litros aprox. ha bebido las últimas 18h?</b> _____	<b>¿Ha comido algo?</b> <input type="checkbox"/> NO <input type="checkbox"/> SI	<b>¿Ha usado protección solar (crema, gafas, gorra...)?</b> <input type="checkbox"/> NO <input type="checkbox"/> SI	

**Marque con una X** la puntuación que considere más acorde **si ha notado...**

	<b>0 Ningún</b>	<b>1 Leve</b>	<b>2 Moderado</b>	<b>3 Intenso</b>
<b>Dolor de cabeza</b>				
<b>Molestias gastrointestinales</b> (dolor de barriga, náuseas, vómitos, poca hambre, flatulencias, gases, diarrea...)				
<b>Fatiga o debilidad</b>				
<b>Mareo, aturdimiento o vértigo</b>				
<b>¿Si ha tenido alguno de estos síntomas, como han afectado a su actividad?</b>	No han afectado	Presentes pero aliviados con ibuprofeno, descanso...	Obliga a parar ascensión	Evacuar a menor altitud

**COMENTARIOS:**

Conforme contestas este cuestionario estas aceptando el uso de los datos siguientes para el estudio realizado con la Universidad de Girona para el Trabajo Final de Grado para conocer la prevalencia del Mal de Altura en los Pirineos y factores asociados.

17.7 Annex 7. Link and QR code

# ¿Mal de altura en los Pirineos?

Ayúdanos a saber si hay Mal de Altura en los Pirineos y cuáles son los factores de riesgo. Una patología que puede afectar a todas esas personas que suben a más de 2.500 m de altitud y se caracteriza por dolor de cabeza, mareo, náuseas, fatiga... entre otros.

Responda esta encuesta una vez finalizada su reciente actividad en alta montaña mediante el código QR o el link.

Serán solo 3 minutos y no se recogen datos personales.

¡Muchas gracias por su tiempo!



<http://bit.ly/maldealtura>

## 17.8 Annex 8. Tryptic information AMS



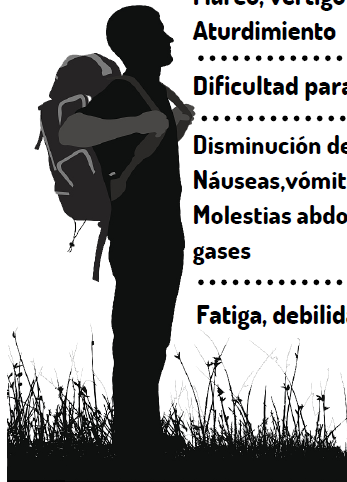
### ¿ QUÉ ES EL MAL DE ALTURA?

Es un término usado para describir diferentes patologías que se pueden desarrollar en altitudes mayores de 2.500m relacionadas con la falta de oxígeno.



### ¿ CÓMO SE PRESENTA?

Dolor de cabeza  
Mareo, vértigo  
Aturdimiento  
.....  
Dificultad para respirar  
.....  
Disminución del apetito  
Náuseas, vómitos  
Molestias abdominales, gases  
.....  
Fatiga, debilidad



### SÍNTOMAS DE ALARMA

- Síntomas anteriores graves
- Alteración del estado mental, disminución de la conciencia
- Ataxia, descoordinación






### TRATAMIENTO

- Reposo y hidratación
- Si cefalea: paracetamol o antiinflamatorios
- Si vómitos: antieméticos
- Si son graves, llamar al 112:
  - Descenso
  - Oxigenoterapia
  - Acetazolamida o Corticoides



### PREVENCIÓN

- Hacer una ascensión lenta 
- Aclimatarse los días previos 
- Buena hidratación 
- Ingesta de carbohidratos



<http://bit.ly/maldealtura>

### ENCUESTA

Ayúdanos a saber si hay Mal de Altura en los Pirineos y los factores de riesgo.

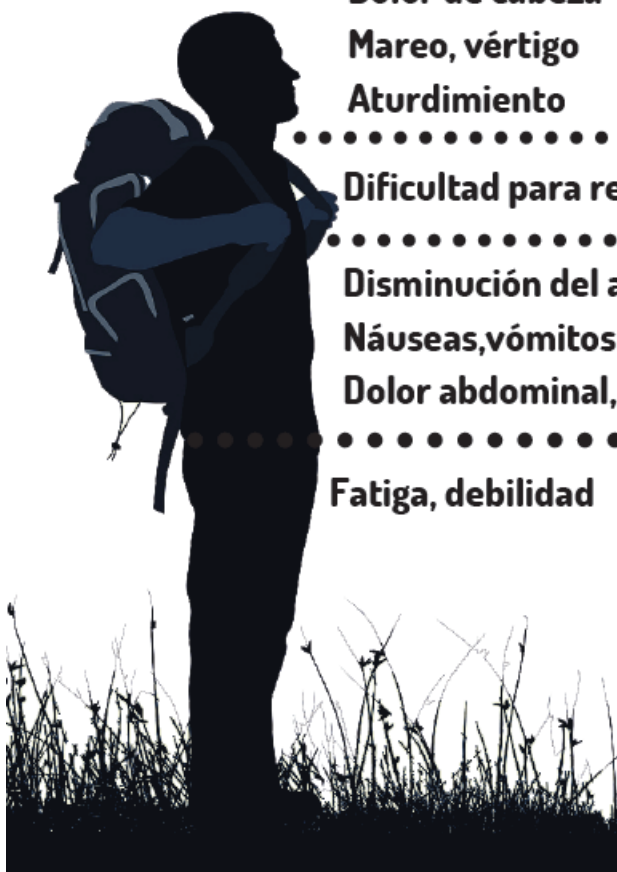
Contesta esta encuesta una vez realizada vuestra reciente actividad en alta montaña, mediante el código QR o el link.

Serán sólo 3 minutos y no se recogen datos personales.  
Muchas gracias por su tiempo.


# ¿QUÉ SABE SOBRE EL MAL DE ALTURA?

Es un término usado para describir diferentes patologías que se pueden desarrollar en altitudes mayores de 2500 m relacionadas con la falta de oxígeno.

**Se puede presentar como:**




- Dolor de cabeza
- Mareo, vértigo
- Aturdimiento
- .....
- Dificultad para respirar
- .....
- Disminución del apetito
- Náuseas, vómitos
- Dolor abdominal, gases
- .....
- Fatiga, debilidad



**Descender si:**

- Síntomas graves
- Alteración estado mental
- Ataxia, descoordinación

 **112**