A Cross Sectional Review: Effects of Dehydration on Subdural Hematoma Risk in Athletes

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A CROSS SECTIONAL REVIEW: EFFECTS OF DEHYDRATION ON SUBDURAL
HEMATOMA RISK IN ATHLETES

A Thesis Presented to the Faculty at the Yale University School of Medicine
In Candidacy for the Degree of Masters in Medical Science

March 2023

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List of Abbreviations
AUC area under curve
BUN blood urea nitrogen
CDM Common Data Model
CI confidence interval
Cr creatinine
CSF cerebrospinal fluid
CT computed tomography
DOAC direct oral anticoagulant
eGFR estimated glomerular filtration rate
EMR electronic medical record
GCS Glasgow Coma Scores
HIPAA Health Insurance Portability and Accountability Act
HR hazard ratio
OMP Observational Medical Partnership
OR odds ratio
ROC receiver operating characteristic
pOsm plasma osmolality
I inconsistency
IRB institutional review board
MD mean differences
MRI magnetic resonance imaging
NCAA National Collegiate Athletic Association
SDH subdural hematoma
TBI traumatic brain injury
U urea
USBLS United States Bureau of Labor Statistics
VKA vitamin K antagonist
YNHH Yale New Haven Health

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Abstract

Subdural hematomas are precedent to nearly all catastrophic head injuries in athletics, and are a leading cause of death and morbidity in sports. While known risk factors exist, cases still occur in young, healthy athletes without clear predisposition—occasionally without a precipitating traumatic event. Athletes are at increased susceptibility for dehydration, and the effects of inadequate fluid status on subdural risk is unknown. This study aims to elucidate the relationship between dehydration during athletic activity and subdural hematoma formation. We propose a cross-sectional study utilizing Yale New Haven Hospital electronic medical records, where we compare hydration status at emergency room admission in athletes with subdural collections to that of matched controls. This study will allow us to further understand the pathophysiology and risk factors of subdural hematomas, as well as provide additional points of prevention especially when it comes to weight class and physique sports, which necessitate dehydration.
Chapter 1 - Introduction

1.1: Background

Sports and athletic activities are a common pastime with varying degrees of investment and competition within all age spectrums of the United States. Data from 2018 suggests that the majority of children aged 6 to 12 played a team sport. In the same year, 7.9 million high school athletes participated in school-sanctioned sports leagues, not including club sports and extracurricular travel leagues. Roughly 500,000 college athletes participated in National Collegiate Athletic Association (NCAA) championships in the 2018/2019 athletic year, not taking into account collegiate participation in sports non-sanctioned by the NCAA, club sports and intramurals. Roughly a quarter of adults are also involved in sports, with 18% of the adult population engaging in some form of physical activity on an average day. In total, an estimated 214 million Americans regularly engage in sports-related activity.

In spite of the multitude of psychological and physical benefits provided through sports, such activities also involve various risks. For example, roughly 2.6 million sports-associated emergency department visits occur each year in athletes aged 5 to 24 years, with the greatest proportion of injuries drawing from football, basketball, soccer, and cycling. Epidemiological data from collegiate athletes suggests that the sport with the greatest rates of injury was American football, with player contact being the major mechanism of injury across all sports. A nationally representative sample of US high school athletes determined that of injuries reported over the span of 16 years, approximately 92% are acute and 8% are attributed to overuse.

Ankle ligament sprains are the most common injury in college athletes comprising almost 15% of all injuries. In high school athletes, the most common overuse injury diagnoses are...
muscle strain and tendonitis\textsuperscript{5}. Ligament sprains are most common (31.7\%), with concussions sustaining 21\% of all acute injury diagnoses\textsuperscript{5}. While rare, catastrophic neurological injuries that may pose semi-permanent to permanent disability or death also occur. Electronic medical record data suggests that up to one third of traumatic brain injury (TBI) is sports-related\textsuperscript{6}. Subdural hematomas (SDH) which describe blood collections between the dura layers of the brain are precedent to roughly 90\% of catastrophic head injuries in American football players, and are a leading cause of death and severe morbidity in many combat sports\textsuperscript{7}. Notably, uncommon cases of SDH formation have been reported in a diverse range of noncontact sporting events as well, such as swimming, marathon running, weightlifting, bicycling, and generic athletic training\textsuperscript{7, 8, 9, 10, 11, 12, 13}.

Acute SDH is most frequently associated with direct head trauma, with blood collection occurring due to brain contusion, or rupturing of intracranial vessels\textsuperscript{7}. Acute SDH constitutes a medical emergency, with autopsy reports demonstrating that as many as half of fatalities occur within 24 hours of cephalic insult\textsuperscript{14}. Bridging vein rupture underlies the majority of sports related SDH\textsuperscript{7}.

However, cases of spontaneous and chronic SDH have also been reported with preceding intracranial hypotension and associated orthostatic headaches\textsuperscript{10, 13}. Intracranial hypotension results from depletion of the cerebrospinal fluid (CSF), which normally offers hydro-mechanical protection to the brain\textsuperscript{15}. In addition to CSF depletion, cases are frequently associated with various other predisposing factors, such as coagulopathy, anticoagulant and antiplatelet therapy, alcoholism, and malignancies\textsuperscript{16}. Furthermore, it is suspected that forgotten or seemingly trivial cephalic impacts may underlie some chronic SDH, with acute subdural formations occurring prior\textsuperscript{16}. Chronic SDH have been reported from injuries sustained during sports, as well as
seemingly benign activities such as sporting without incident, usage of vibrating exercise equipment, and roller coaster rides \(^7\).

While chronic SDH can occasionally present without symptoms and be diagnosed incidentally through brain imaging, the presentation may vary greatly \(^18\). Headaches, seizures, amnesia, confusion, difficulties speaking, swallowing, and ambulating; and focal weaknesses are known symptoms of chronic SDH \(^19\). Initial symptoms of acute SDH include loss of consciousness, headache, vomiting, dizziness, and seizures, with potential later manifestations of decreased consciousness with intervals of lucidity, paresis, and progression to coma \(^7\). Some players may have persistent headaches after injury, which may be suggestive of a thin subdural effusion \(^7\).

Although asymptomatic cases may be managed with conservative measures such as observation, hydration manipulation, or reversal of coagulopathy; neurosurgery remains the mainstay of treatment cases \(^19\). In acute patients, urgent decompressive craniotomies involving surgical hematoma evacuation are often indicated \(^7\), with subsequent multidisciplinary critical care \(^20\). Acute traumatic SDH have estimated mortality rates of between 40-60%, with significantly greater chances of survival with prompt intervention \(^21\). However, complications often affect survivors. Recurrence rates are estimated to occur in between 2 to 37% of patients following neurosurgery \(^22\). Lifelong health consequences, such as decreased cognitive function and emotional, psychosocial, and mental health outcomes, may also persist despite surgical resolution \(^23\).

Compared to the general population, acute SDH has specific considerations in active people. For example, young athletes have less subdural space than elderly patients, which results
in a more rapid elevation of intracranial pressures and advancement of clinical severity \(^{24}\). Clinical outcomes may be further worsened due to an increased rate of coup and contrecoup injuries in athletics \(^{7}\). Athletes also commonly neglect minor head trauma and return to play preemptively, which increases the risk of subsequent head trauma by fourfold, as well that of catastrophic brain injuries such as SDH \(^{25}\). Second-impact outcomes from cerebral edema frequently include severe neurological deficits and fatality \(^{26}\). For individuals that do seek and receive appropriate medical counseling, significant risks still exist for return-to-play. Following craniotomy, less than half of physicians endorse return-to-play within one year \(^{27}\). Players may be subject to medical disqualification or voluntary retirement from sport following TBI \(^{28}\), which presents with a severe postcareer mental health burden due to rapid changes in athletic identity and lifestyle, as well as reduced access to social networks \(^{29}\). These unique concerns necessitate additional measures in order to ensure safe, sustainable athletic careers in both the hobbyist and elite sportsman.

Although frequently overlooked compared to musculoskeletal and neurological injuries, athletes are also particularly vulnerable to dehydration. For example, training in adverse environments can produce as much as 10 L of fluid loss per training day \(^{30}\). In prolonged sporting activities such as American football and individual endurance sports, average water losses are estimated to be 1.52 L/hr and 1.28L/hr, respectively, with extreme body mass losses of as high as 12% due to net water losses observed in triathletes \(^{31}\). Studies in hot climates indicate that as many as 98% of professional players demonstrate moderate to severe hypohydration prior to practice \(^{32}\), while a quantitative systematic review suggests that pre-exercise fluid depletion occurs at a prevalence of 55.6% of recreational soccer players \(^{33}\).
Furthermore, dehydration is a common competition preparation tactic for physique sports and sports with weight classes, such as wrestling, weight lifting, and mixed martial arts (MMA). A review of combat athletes detected rapid weight loss techniques in roughly 50% of practitioners, with greater prevalence and severity associated with higher levels of competition. Although the majority of athletes reduce only 2-5% of their total body weight, roughly 40% of competitors will reduce 5-10% of their body weight rapidly. Notably, a significant number of responders have reported cutting greater than 10% of their body weight within a week of weigh ins. Rapid weight loss techniques including fluid restriction and increasing bodily secretions are reported in 40 to 90% of high school, collegiate, and international competitive wrestlers. A survey of professional MMA fighters determined that 98% cut weight prior to matches, with the most prevalent methods in descending order being food restriction, sauna, increased training, water loading, and salt baths. Additionally, a small percentage also reported usage of induced vomiting, diuretics, water restriction, and other extreme measures. Weight, fluid and electrolyte manipulation are also extremely common in competitive physique sports, such as bodybuilding, and thus confer similar risks.

Mild dehydration between 1% to 3% of fluid loss by body weight results in decreased cognitive and athletic performance that may confer concussion-like symptoms such as headache, dizziness, and decreased ability to concentrate. Another study examining mild to moderately dehydrated athletes (defined as less than 5% of total body weight lost as fluid) found a greater severity and variety of symptoms compared to a euhydrated group, including balance problems, slowed movements, difficulty remembering, and drowsiness and fatigue. At severe levels of dehydration, syncope, cardiovascular compromise, exertional heat exhaustion, and renal dysfunction and injury are known to occur. A hypovolemic state may also result in a reduction
of CSF fluid and subsequent intracranial hypotension. While continuous fluid intake is efficacious at preventing symptomatic dehydration in athletes, those with excessive uncompensated losses (such as those with acute weight cutting needs or prolonged activity) may be unable to mitigate volume depletion, which makes them more vulnerable to possible sequelae.

1.2: Statement of the Problem

In athletes diagnosed with a SDH without an identified preceding head injury, such as in the case of a 37-year old male marathon runner with no past medical history or risk factors, it has been hypothesized that severe dehydration may precipitate systemic hypotension and subsequent intracranial hypotension, which may facilitate the formation of a SDH. In fact, cases of spontaneous and chronic SDH have been reported with preceding intracranial hypotension and associated orthostatic headaches. The risks may be further compounded by post-exertional hypotension, which becomes more profound with prolonged and intense activity. Because SDH is often associated with an obvious traumatic brain injury, dehydration as a risk factor may be overlooked—however, its potential as a contributing factor may be clinically important.

Evidence suggests that mild exercise-related dehydration reversibly alters memory, balance, and coordination, which may predispose players to injury. Additionally, according to Maughan et al, the average marathon runner loses 6.5% of plasma volume over the course of a race. Brain imaging after acute dehydration demonstrates increased ventricular volume, along with reversible decreases in global brain volume, including gray and white matter volume, hypothalamus and thalamus volume, and cortical thickness. Such intracranial changes with dehydration may theoretically allow for increased deceleration forces to the brain following unapparent cranial impacts in athletes, which may explain spontaneous formation in healthy
young sportsmen with no apparent trauma, and a potential increased risk for SDH in athletes with traumatic brain injury.

**Figure 1.** Proposed impact of clinical dehydration on catastrophic head trauma and subdural hematoma risk.

The role of hydration status and initial SDH risk in athletes has not been directly investigated to date. In parturient women, perilabor dehydration is believed to increase risk of SDH as well as a prodromal headache after dural puncture. Intracranial venous sinus thrombosis, which is often associated with subsequent hemorrhage, has been linked to hypohydration as a predisposing risk factor. Preexisting clinical data also demonstrates that 20-45% of patients with spontaneous intracranial hypotension develop SDH as a complication, although the proportion of these patients who present due to severe dehydration is not exactly known. Plasma osmolality has also been utilized as a proxy for hydration status, and associated with an increased risk of mortality in SDH patients, and may suggest a relationship between hydration status and SDH severity. Similarly, severe hypernatremia may indicate water
depletion in relation to serum sodium content and subsequent dehydration, but excludes conditions in which both sodium and total body water are depleted \(^{49}\). Hypernatremia has been causally linked to SDH in pediatric populations, although the exact significance is unclear \(^{50}\). In hospitalized patients with traumatic chronic SDH, dehydration at pre admission greatly increases the odds of SDH recurrence after neurosurgical evacuation \(^{51}\). While a vague connection is supported by the literature, additional research is merited.

1.3: Goals and Objectives

The goals of this retrospective cross-sectional study are to elucidate a potential association between hydration status and SDH formation in athletes. This will be accomplished by comparing fluid status between athletes diagnosed with SDH after physical activity, and matched controls without this condition within the Yale New Haven Health electronic medical record database.

1.4: Hypothesis

We hypothesize that there will be a statistically significant increase in the odds ratio of SDH formation in athletes in the setting of clinical dehydration compared to adequate fluid status at medical evaluation. We additionally predict that the severity of SDH, as measured by three independent secondary variables: mean effusion size, Glasgow Coma Score, and mortality within 30 days, will be elevated in the exposure group. We further predict that the preceding sporting event category (such as combat, contact, and non-contact) and suspected mechanism of SDH (such as direct head trauma, and iatrogenic) will influence SDH formation rates in both hydrated and dehydrated athletes. Finally, we predict that within the dehydrated subgroup, the odds ratio of developing SDH will increase with the severity of dehydration.

1.5: Definitions
**Athlete:** A person who routinely trains in sports, exercises, or games requiring physical strength, agility, and or stamina. For the purpose of this study, we will consider all persons who regularly partake in these activities for at least 60 minutes a week.

**Combat sport:** A one-on-one contact sport in which contestants simulate components of hand-to-hand or weapon combat during play. Combat sports include traditional martial arts (i.e. taekwondo), boxing, kickboxing, muay thai, wrestling, and fencing.

**Extreme sports:** Activities that involve high risks due to high velocities or potential for lengthy falls. Examples include mountain biking, skateboarding, and ice climbing.

**Contact sport:** Sports that cannot be undertaken without physical contact between players. Projectiles and equipment also frequently make contact with players. Combat sports technically are a subset of full-contact sports. Examples of full contact sports include American football and rugby, which require tackling of players.

**Non-contact sport:** Sports in which participants should have no means of making contact, due to rulesets as well as physical separation between players. Examples include swimming, cycling, and running.

**Dehydration:** Fluid depletion of clinical significance. For the purposes of this study, we will be defining dehydrated persons as having a blood urea nitrate (BUN) to creatinine ratio of >20.

### 1.6: References


**Chapter 2 - Literature Review**

2.1: Introduction
To evaluate the existing literature regarding subdural hematomas and fluid volume status, a systematic review of the literature was conducted in December 2022 and March 2023. The databases PubMed, OVID, and WebOfScience were utilized. The search history spanned from the earliest publications to those released up to March 2023. Search terms included “subdural hematoma” OR “subdural hemorrhage” OR “subdural collection” OR “subdural haematoma” OR “subdural bleeding”, AND “dehydration” OR “hypohydration” OR “volume depletion” OR “hypernatremia”. Only full articles available in the English language pertaining to human studies were subject to review. All results that were not research studies, systematic reviews, or large scale meta-analyses were excluded. Our search was specifically conducted for papers published between January 2012 and March 2023.

In March 2023, our PubMed search resulted in 12 initial results, which demonstrates the paucity of foundational research on this topic. The Web of Science Core Collection resulted in 12 results. The OVID database search resulted in 25 results with the initial search terms, many of which were duplications. Articles were further selected based on relevance to the primary research question. We found 3 extant studies that addressed the relationship between hydration status and SDH.

2.2: Review of relationship between dehydration exposure and SDH risk

A meta-analysis of the literature conducted by Ali et al in 2012 examined a potential relationship between severe hypernatremia and SDH in the pediatric population. This study excluded all persons over the age of 7 years and cases in which antecedent intracranial pathology caused the hypernatremia. Only cases in which the sodium level was >150 mmol/L and neurological findings were validated through radiodiagnostic, surgical, or postmortem examination were included.
In total from the years 1950 to 2007, there were 124 cases from 31 different articles in which children with hypernatremia were evaluated intracranially. While 67 of the cases did not provide specific serum sodium levels or demographics, the overall average of the 57 remaining cases were 40.7 weeks old, with average sodium levels of 173 mmol/L. 112 cases of hypernatremia were noted to occur prior to hospital admission, while 12 cases occurred inpatient in a controlled setting without any prior trauma. Of these 124 cases, 7 children had developed SDH after hypernatremia began outside of the hospital. While no injury or abuse was recorded, 2 of the cases were associated with neglect. Notably, all 7 cases were due to total water volume depletion—hypernatremia was caused by gastrointestinal losses in 6 cases, while 1 case was caused by dehydration following starvation. Also of note is that while no SDH cases occurred in the patients who developed hypernatremia in the hospital, all of their cases were due to exchange transfusion or accidental hypertonic formula—there was no volume depletion.

The authors extend that although there may be an association between hypernatremia and subsequent SDH formation, there is low quality evidence to suggest that it is a direct cause of SDH. However, they do note that there was an increasing frequency of SDH (and all intracerebral hemorrhage types) with increased degree of hypernatremia.

The study strengths include its accounting for patient-specific demographics and history, potential confounding variables (such as presence of trauma and mechanism of hypernatremia) as well as taking into account temporality of exposure which may otherwise play a huge confounder when it comes to cause and effect studies. However, significant selection bias occurs with the utilization of a case series, including a non-response bias of cases that are not publicly reported. There are also no statistical methods employed to calculate risk, odds ratio (OR)
or association of the exposure to the outcome, and they would likely not maintain much external validity due to the issues discussed above.

A retrospective cross-sectional study conducted by Wang et al examined the relationship between serum BUN values in patients already diagnosed with chronic SDH, and SDH recurrence after burr hole irrigation. Patients were diagnosed by CT or MRI by neurosurgeons who were blinded to the study between 2014 and 2019 at the First Affiliated Hospital of Wenzhou Medical University in China. However, exclusion was based on those not requiring burr hole irrigation, pediatric patients under the age of 18, severe epileptics, those with severe renal and blood diseases, those who did not receive pre and post operative laboratory workups, and cases with hospital mortality. While 676 cases presented during this time period, only 653 were eligible for the study—patients receiving 2 operations counted as 2 cases.

In terms of patient characteristics, researchers noted age, gender, comorbidities, preoperative and postoperative laboratory values including BUN, postoperative medications, location of hematoma, and Glasgow Outcome Score after operation. All patients underwent the same procedure (burr hole irrigation under general anesthesia) and received follow up CT scans 3 times at 48 hours, 6-7 days, and 3 months after the procedure. Patients were divided into recurring and non-recurring groups respectively, then analyzed for the previously discussed characteristics variables in relationship to occurrence.

653 total cases were included in the analysis, including 561 men and 92 women. The ages ranged from 21 to 100, with the median age being 72 years old. 96 of the SDH cases were reoccurring, and include 16 cases with 2 operations. There was a statistical difference between pre and postoperative groups on serum BUN concentration (P = 0.001 and P < 0.001, respectively), with P = 0.003 between quartiles. The preoperative BUN levels were significantly
elevated compared to postoperatively in the non-recurrence group (P < 0.001) while there was no statistically significant difference in the recurrence group. Notably, within the recurrence group, patients were also older, and had lower serum concentrations of leukocytes, neutrophils, platelets, and fibrinogen, which may have affected pathophysiology.

Post-operative BUN levels were further split into 4 quartiles (< 4.0 mmol, 4 < 4.9 mmol, 4.9 < 6.4 mmol, and >6.4 mmol) and examined for relationship to outcome and other variables. The top quartile (>6.4 mmol BUN) had the most patients with moderate disability at discharge (22/157), and most recurrences of SDH (P = 0.012). Furthermore, it was statistically calculated to be a risk factor of SDH recurrence with an unadjusted odds OR of 3.315 (95% CI:1.711-6.423, P < 0.001) compared to postoperative BUN levels of <6.4 mmol. This was adjusted for confounders including demographic information, alcohol intake, smoking, comorbidities, medications, and other laboratory markers— the highest BUN quartile remained independently and significantly associated with SDH recurrence among 3 separate models (model 1: OR = 2.892, 95% CI:1.463–5.717, P = 0.002; model 2: OR = 2.939, 95% CI:1.480–5.836, P = 0.002; model 3: OR = 3.069, 95% CI:1.488–6.330, P = 0.002). Furthermore, there was no multicollinearity detected between independent variables. After logistic regression, increased preoperative BUN levels were also associated with recurrence of SDH. As BUN may reflect renal function, the authors also measured and analyzed the effects of creatine on SDH recurrence, which had no impact.

The study has multiple limitations: most glaringly is its selection bias due to its single-center clinical design, which reduces its generalizability. Despite the retrospective nature of the study, the authors analyze potential confounding factors of SDH predisposition with rigorous statistical methods, such as demographic information, comorbidities, medications, and other
laboratory measurements. The study also boasts a robust sample size and strong postoperative follow up procedures at 3 different time points. BUN is associated with protein intake and catabolism, nitrogen production, and neurohormonal activation, but may also indicate a patient’s fluid status, especially when combined with creatinine (Cr).

A study by Mainka et al published in 2022 similarly examined the effect of dehydration status on chronic SDH recurrence risk after surgical evacuation. Their main definition of dehydration is a serum urea over Cr (U/Cr) level > 80, expressed as a binary variable. Additionally, all available biomarkers of dehydration used were urea (> 7.5 mmol/L), serum sodium (>145 mmol/L), and estimated glomerular filtration rate (eGFR) >30. All consecutive patients within the medical records at the University Hospital Bonn were retrospectively screened from the years 2015 to 2019. All patients underwent single burr hole craniotomy with irrigation under general anesthesia, with neuroradiology follow up after 3 weeks with a postoperative CT scan.

A total of 265 patients with chronic SDH requiring surgery between 2015 and 2019 were identified, with 32 (12%) having a recurrence requiring follow-up surgery. Furthermore, 9 of the 265 total cases (3%) were found to have a U/Cr >80 at time of admission. Multivariate analysis showed that dehydration on admission was a significant and independent predictor for the development of SDH recurrence (p = 0.002, OR 10.3, 95% CI 2.4–44.1). Additionally, diabetes mellitus (p = 0.02, OR 2.7, 95% CI 1.2–6.5) and a preoperative midline shift > 5 mm (p = 0.003, OR 3.3, 95% CI 1.5–7.5) were also associated with increased odds ratios of SDH recurrence. However, pre-existing disease, location of SDH, or presence of septations was not associated with recurrence.
The study has several limitations. There is the retrospective nature of the study, which gives limited insight into the actual relationship of the exposure and outcome. It is a single-center data collection study which limits the generalizability to outside populations. An extremely small number of cases were found to have the exposure (n=9). Additionally, as there were not many cases, the authors did not list any exclusion criteria, which constitutes a large degree of confounding. For example, the dehydrated group defined by U/Cr > 80 all had admission eGFRs < 30 mL/min, meaning that there may have been a large amount of nephrogenic disease confounding SDH formation risk. While the authors attempted to take into account various patient characteristics, clinical data, and laboratory values, they did not utilize any statistical modeling to compensate for missing record data, which made much of the secondary analyses very weak and not statistically significant.

**Table 1.** Review of studies examining hydration status and SDH.

<table>
<thead>
<tr>
<th>Author &amp; publish date</th>
<th>Measure of Hydration Status</th>
<th>Population</th>
<th>Study Design</th>
<th>Summary of notable Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali et al, 2012</td>
<td>Serum sodium</td>
<td>Children &lt;7 years old with Na &gt;150 mmol/L N = 124</td>
<td>Meta-analysis of case reviews</td>
<td>Increased likelihood of SDH with increased severity of hypernatremia (not statistically supported)</td>
</tr>
<tr>
<td>Wang et al, 2020</td>
<td>Blood urea nitrate (BUN)</td>
<td>Patients above 18 years old diagnosed with chronic SDH requiring surgical evacuation at Wenzhou Medical University</td>
<td>Retrospective case control</td>
<td>Elevated postoperative BUN (&gt; 6.4 mmol/L) is associated with increased OR of SDH reformation after burr hole irrigation (OR: 3.315 95% CI:1.711-6.423, P &lt; 0.001).</td>
</tr>
</tbody>
</table>
Table 1: Clinical characteristics of study population

| Mainka et al, 2022 | Urea Creatinine ratio (U/Cr) | All patients diagnosed with chronic SDH requiring surgical evacuation at University Hospital Bonn | N = 265 | Retrospective case control | Elevated U/Cr > 80 (dehydration) is preoperatively associated with SDH reformation after burr hole irrigation (OR 10.3, 95% CI 2.4–44.1, p = 0.002) |

2.3: Review of relevant methodology: measurements of hydration status

Unfortunately, there is no gold standard measurement for dehydration. The diagnosis is frequently made on a clinical basis with physical exam procedures, which produce subjective findings and cannot be standardized for a reliable retrospective study design. Dehydration also produces many urine and serologic composition changes that can be detected with common laboratory measurements. We examine several objective markers of dehydration that can be used within the acute setting and reliably reported in the EMR.

Plasma and Serum Osmolality

A narrative review of the literature by Barley et al was conducted for current methods of assessing hydration in athletes. Plasma osmolality (pOsm) was immediately criticized as not being a direct measure of cellular hydration, as half of all plasma volume lost is recovered within one hour after exercise even without fluid ingestion. The authors also noted that pOsm is heavily confounded by food intake, due to fluid shifts from the vasculature to the gastrointestinal system. Baselines vary greatly per individual, which complicates its usage in standardized settings. pOsm nonetheless is still touted as the “gold standard” measurement in some labs, although there is some controversy over its utility given its cost and analytical complexity. Of note, there is wide variation in the usage of serum osmolality (mOsm) calculations across
laboratories— even with a standardized cutoff point of >295 mOsm which is widely accepted, this carries only an 85% sensitivity and 59% specificity for dehydration.

**Serum Sodium**

Hypernatremia, defined as serum sodium (Na) >145 mmol/L, contributes to the majority of pOsm but gives minimal data on the other electrolytes. It has the additional benefit of being included in common laboratory draws, but is less accurate than pOsm in predicting clinical dehydration. The above limitations of pOsm all apply to Na readings, especially due to losses associated with diaphoresis.

**Blood Urea Nitrate to Creatinine Ratio**

BUN/Cr is ubiquitously utilized as an objective marker for dehydration and prerenal azotemia in research studies with a threshold of >20 signifying hypohydration. Notably, the physiologic ratio tends to rise above 10:1 in states of dehydration.

Despite its longstanding usage within the clinical and research setting, there seems to be a paucity in literature contesting its validity as a measure of hydration status. There are some small studies that corroborate its strengths in clinical dehydration testing. A small study conducted on long term care residents with oropharyngeal dysphagia (n=28) found significant elevations in BUN/Cr ratios in patients with reduced urine output (<800 mL) compared to euhydrated patients (p = 0.001). However, of note, this physical exam finding has limited sensitivity (0.17, 95% CI (0.03 to 0.60)) despite being specific (0.87, 95% CI (0.13 to 1.00)) for dehydration. In hospitalized elderly persons (n=59), elevations in BUN/Cr levels were significantly correlated with clinical parameters of dehydration such as heart rate (r=0.300; p = 0.021), capillary refill (r = 0.379; p = 0.013), and systolic blood pressure (r = -0.261; p = 0.046), on post-ROC analysis. BUN/Cr was also positively correlated with pOsm for dehydration findings (AUC: 0.820, p = 0.046).
0.013). No data on sensitivity or specificity for BUN/Cr for dehydration testing could be found, although potential confounding variables are noted as discussed below in section 2.4.

**Urine Variables**

Various objective urine variables were also examined by Barley et al, including urine specific gravity (USG) >1.020, and urine osmolality (uOsm) > 700 mmol/kg. These variables were noted to be influenced by diet, drugs, illness, and fluid intake. They correlated poorly to serum measurements due to hormonal fluctuations, often giving false indications of euhydration on rapid rehydration studies. This is corroborated by a systematic review of the literature conducted by Hooper et al, who examined the diagnostic accuracy of urine tests in elderly populations for water loss dehydration. USG was reported within 12 different studies, with the minimum threshold for dehydration ranging from > or = 1.020 to >1.035. All studies reported low sensitivities (0.00 - 0.46) regardless of USG cutoff values, as well as modest to high specificities (0.50 - 1.00). uOsm was reported in 18 studies, with the minimum threshold for dehydration ranging from > 600 mOsm/kg to > 1000 mOsm/kg. All studies similarly showed low sensitivity that did not improve despite increasing cutoff values with the exception of one study (0.00 - 0.80). The specificities were also highly variable (0.45 - 1.00), but post hoc ROC (receiver operating characteristic) analysis demonstrated uOsm to have poor diagnostic value as a stand alone test for dehydration.

**Table 2.** Review of objective measures of dehydration and utilization in clinical research.

<table>
<thead>
<tr>
<th>Plasma Osmolality (pOsm) and Serum Osmolality (mOsm)</th>
<th>Serum Sodium (Na)</th>
<th>Blood Urea Nitrate to Creatinine ratio (BUN:Cr)</th>
<th>Urine specific gravity (USG)</th>
<th>Urine Osmolality (uOsm)</th>
</tr>
</thead>
</table>
2.4: Review of Studies to Identify Possible Confounding Variables

Confounders of predictor variable

The existing research contains much information on modifying variables that may act as confounders within our study. The popular literature has many established causative factors for SDH, including head trauma. There have also been many popularized risk factors for SDH
without overt trauma, including elderly age, and coagulopathies (which may be induced by medications, underlying comorbidities and conditions, vascular abnormalities, and alcoholism). We attempt to examine some of these possible confounding variables to greater detail.

A case-control study (n = 10,010) examined the association of antithrombotic drug use with SDH hematoma risk using population-based epidemiological data from Denmark. Increased SDH risk was associated with current use of low-dose aspirin (1.24 adjusted OR, 95% CI (1.15-1.33)), direct oral anticoagulants (DOAC) (1.73 adjusted OR, 95% CI (1.31-2.28)), and vitamin K antagonists (VKA) (3.69 adjusted OR, 95% CI (3.38-4.03). Concurrent usage of VKA and an antiplatelet predictably resulted in increased risks, depending on the agents combined.

A national case-control study conducted in Taiwan (n = 14,026) examined risk factors in elderly patients with minor head injuries diagnosed with chronic SDH at least 5 years later after exposure. 11 comorbidities were examined as independent risk factors, as well as age and sex. Interestingly, diabetes mellitus, hypertension, chronic liver disease, heart failure, atrial fibrillation, peripheral artery disease, and deep vein thrombosis did not confer statistically significant changes in the cox regression hazard ratios (HR) for SDH formation. Interestingly, chronic kidney disease in patients >75 years old conferred a decreased risk (HR 0.5, 95% CI (0.27-0.98), P = 0.042), as did ischemic heart disease in patients < 75 years old (HR 0.57, 95% CI (0.39-0.83), P = 0.004). The authors identified additional risk factors as hydrocephalus in patients >75 years old (HR 2.76, 95% CI (1.41-5.41), P = 0.003).

However, these findings were conflicting with the incidence data from the national Danish studies, where SDH cases were associated with higher levels of comorbidity. This pertained especially true to alcohol use disorder (17.6% cases, 4.6% controls), hypertension (54% cases, 46.3% controls), stroke (14.2% cases, 6.8% controls), epilepsy (6.6% cases, 1.8%
controls), dementia (5.8% cases, 2.7% controls), chronic renal failure (2.9% cases, 1.5% controls), chronic liver disease (2.6% cases, 1.0% controls), and coagulopathy (0.5% cases, 0.2% controls) \(^{16}\). All comparisons were statistically significant (P < 0.001) \(^{16}\).

Male sex has also been reported as a popularized risk factor in the popular literature, hypothesized to be due to an increased exposure to head trauma and alcoholism \(^{18}\). Interestingly, we found our reported studies to have an overwhelming male predominance in their sample sizes irregardless of reporting methods, commensurate with the common consensus. Tseng et al confirm this in Taiwanese national population: patients with minor head injuries who have developed SDH are predominantly male (65.7% versus 49.7%, \(P < 0.001\)) \(^{17}\). However, Marshman et al, while able to validate the male bias for chronic SDH, found that history of trauma and alcohol abuse were not statistically different between sexes \(^{19}\).

**Confounders of measurement**

The BUN/Cr ratio can become elevated due to basic physiologic mechanisms non-related to dehydration \(^{10}\). It can become elevated due to overproduction of BUN, which is produced in the liver as a byproduct of endogenous protein catabolism, with levels correlating to protein intake \(^{20}\). Elevations in BUN are associated with renal disorders (such as chronic kidney disease and kidney stones), congestive heart failure, dehydration, fever, shock, and gastrointestinal bleeding \(^{20}\). However, elevated BUN can also occur during pregnancy \(^{20}\). Decreased production of BUN is commonly observed in cases of trauma, surgery, severe liver disease, and malnutrition, as well as opioid and anabolic steroid use \(^{20}\).

While many of these confounding factors may be accounted for through exclusion measures in a study, dietary variance of protein intake makes this theoretically complicated. A 2014 systematic review and meta-analysis conducted by Schwingshackl and Hoffmann
compared the effects of high protein regimens versus normal protein diets on blood urea measurements in people with no underlying renal dysfunction \(^{21}\). Among 13 studies (n = 910) with minimum interventions of 1 week and differences in protein intake between comparison groups >5%, mean differences (MD) in serum urea were altered significantly (MD: 1.75 mmol/l, 95% CI (1.13 to 2.37), p<0.001) \(^{21}\). The authors noted significant inconsistency (I\(^2\)=88%), especially depending on the degree of protein intake \(^{21}\).

The BUN/Cr ratio may also become elevated due to decreased Cr levels \(^{20}\). While Cr is produced at a stable rate within individuals as a product of muscle metabolism, there are many variable factors that influence its levels within the body \(^{20}\). Increased levels of lean skeletal mass, male sex, red meat intake, and younger age ranges are well known to be associated with higher Cr serum levels \(^{22}\). Elevated glomerular filtration occurs during pregnancy, which accelerates Cr clearance from the bloodstream \(^{23}\), while renal pathologies result in decreased Cr clearance from the bloodstream \(^{20}\). Famously utilized in athletics are creatine supplements, which have controversial effects on markers of kidney function. A 2019 meta-analysis conducted by de Silva et al including 15 studies demonstrated that creatine supplementation negligibly altered serum Cr levels in healthy individuals (MD = 0.48, 95% CI (0.24-0.73), P=0.001) \(^{24}\). However, given the notable variance in dosing and study protocols, the authors noted inconsistencies (I\(^2\)=22%), with increased serum Cr occurring with increased dosages \(^{24}\).

**Table 3. Review of confounding factors of BUN/Cr**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Increased protein intake</td>
<td>- Increased protein intake</td>
<td>- Creatine monohydrate supplementation</td>
</tr>
<tr>
<td>- Renal disorders</td>
<td>- Renal disorders</td>
<td>- Male sex</td>
</tr>
<tr>
<td>- Urinary outflow obstruction</td>
<td>- Urinary outflow obstruction</td>
<td>- Increased lean skeletal mass</td>
</tr>
<tr>
<td>- Congestive heart failure</td>
<td>- Congestive heart failure</td>
<td>- Increased red meat intake</td>
</tr>
<tr>
<td>- Dehydration</td>
<td>- Dehydration</td>
<td>- Younger age</td>
</tr>
<tr>
<td>- Fever</td>
<td>- Fever</td>
<td></td>
</tr>
</tbody>
</table>
The existing literature does not supply sufficient information regarding the effect of hydration status on SDH risk in the athletic population, which merits additional exploration. The meta-analysis conducted by Ali et al in 2012 suggests that dehydration in the state of severe hypernatremia is associated with an increased incidence of SDH in the pediatric population, but lacks rigorous statistical methods to achieve a cogent narrative. Wang et al and Mainka et al demonstrated that preoperative dehydration, shown through elevated BUN and U/Cr levels, is associated with increased post-surgical chronic SDH recurrence rates compared to euhydrated patients with SDH. Overall, there is a paucity of research regarding the statistical effect of hydration on primary SDH risk, and further research is needed to elucidate this relationship.

The current studies examined additionally highlight a lack of a highly validated objective measure of hydration status for clinical research. Although pOsm is utilized as a gold standard within some research labs and is sensitive for dehydration, it lacks specificity, is analytically complex, and is an expensive tool compared to other options. It is therefore unlikely to be ubiquitously available within the EMR. Na is more likely to be available within the EMR due to its overall accessibility and utilization as a clinical laboratory marker in the acute setting, but is less accurate than pOsm. BUN/Cr is a validated biochemical measure of dehydration and has the similar advantage of high accessibility and utilization within the acute clinical setting, as well.
as within retrospective research models. While several confounders for BUN/Cr as a dehydration metric exist, they may be negated through rigorous exclusion criteria in an observational study design. However, sensitivity and specificity data for BUN/Cr as a standalone reporting method has yet to be conducted. In addition to exclusion criteria, confounding and modifying variables will be further isolated through statistical multivariate analysis.

The novelty of this study originates from its usage of multiple sites, imposition of rigorous exclusion factors and statistical methods to account for retrospective bias, and focus on BUN/Cr as an objective marker of dehydration in relation to primary SDH risk. With the information explicated from this research, extant gaps in literature from previous studies may be answered. This may be used to better inform hydration guidelines during athletic activity, as well as prognostication in cases of SDH.

### 2.6: Chapter 2 References

Chapter 3 - Materials and Methods

3.1: Study Design

To elucidate a potential relationship between hydration status and subdural hematoma risk in athletes, we will be conducting an analytical cross sectional study.

The study population will consist of healthy athletes who have been diagnosed with SDH via CT or MRI post-athletic activity. Matched controls will be selected via convenience sampling.
for athletes who presented to acute care (such as the emergency room or urgent care center) for neurological concerns post-athletic activity, but have not been diagnosed with SDH. Both groups will consist of patients who have presented to a hospital within the Yale New Haven Health (YNHH) network within the last 30 years, pending available data within the electronic medical record (EMR). The YNHH system includes all sites.

As the overall prevalence of SDH is relatively rare in the United States, all consecutive patients within the YNHH EMR that meet selection criteria will be utilized for the study group. Exclusion factors include patients with (1) underlying non-iatrogenic coagulation disorders (e.g. liver failure and bleeding diathesis), (2) prior causal neurosurgical and cranial procedures, (3) prior diagnosis of subdural hemorrhage, (4) prescribed anticoagulant drug usage, (5) persons below the ages of 13 years old and above the ages of 65 years old, (6) alcohol use disorder, and (7) significant confounders of BUN/Cr levels (congestive heart failure, gastrointestinal bleeding, renal dysfunction and dialysis, urinary tract obstruction, pregnancy, and severe liver disease). These criteria ensure that we are better able to isolate the potential etiology of hydration status on SDH formation in healthy athletes with no underlying predisposing risk factors.

3.2: Subject Protection and Confidentiality

Approval from the Yale University Institutional Review Board (IRB) will be obtained prior to the start of any study activities. As the study does not exclude persons under the age of 18 years old, ancillary approval from the Pediatric Protocol Review Committee must be obtained prior to IRB approval.

As the study requires widespread EMR review and poses minimal risk to subjects, a Waiver of All Consent will also be requested. In the case that the Waiver of All Consent is denied, individual consent to access EMR data will be solicited electronically through platforms
approved by the Yale University IRB: REDCap, Oncore, and Hugo. As Health Insurance Portability and Accountability Act (HIPAA) regulations apply to medical records for 50 years post death; individual requests and permission for medical record data from the deceased's' next of kin is needed. In cases where contact with said person cannot be made, we will certify to the healthcare facility that the request is for research purposes and that the individual is deceased.

Researching personnel must similarly receive HIPAA authorization and Human Subject Protection Training prior to the initiation of EMR review. To further prevent the potential violation of protected health information, data sets will be deidentified and coded during the collection process.

3.3: Recruitment

Participants for the cross sectional study will be selected and recruited based on the inclusion and exclusion criteria above via systematic convenience sampling. Matched controls will similarly be subject to specific inclusion and exclusion criteria as previously delineated, with random sampling applied to the population.

The independent variable is subdural hematoma formation, which will be operationalized dichotomously. In urgent and emergent settings, SDH is most commonly diagnosed with a CT and is regarded as the standard of care, although MRI is also utilized in detection and evaluation. Patients will thus be stratified by presence of SDH based on CT and MRI findings, as well as post-mortem intracranial examination.

The dependent variable is hydration status, which lacks universal clinical guidelines for definition and diagnosis. Most commonly, physical exam findings and history are used to identify hypovolemic patients in the clinical setting; however, many findings are nonspecific leading to overdiagnosis, and examination is highly subjective and varies by provider. As such,
we propose laboratory values as more objective measures of dehydration. A systematic review of over 24 studies established that serum osmolality >295, BUN/Creatinine (BUN/Cr) >20, hypernatremia, and acute body weight changes are all effective at identifying water-loss dehydration. In an acute setting, body weight differentials may be unobtainable or unreliable. BUN/Cr levels >20 have been found to be more sensitive than hypernatremia as stand-alone markers of dehydration, which makes this laboratory value more preferable for our research purposes. As neurological symptoms may be caused by electrolyte and metabolic abnormalities requiring workup with a basic or comprehensive metabolic panel, we anticipate point of care BUN/Cr and sodium levels to be commonly reported in the EMR for our population of interest. Normal ratios in a healthy, adequately hydrated individual range from roughly 10-15. We will therefore proceed with definitions of a BUN/Cr ratio >20 equating to hypovolemia, and ratios of less than or equal to 20 being adequately hydrated. Hydration status will also be operationalized as dichotomous for the purpose of primary hypothesis testing.

Control variables are delineated in the exclusion factors above to ensure that all participants are healthy athletes with no underlying predisposing risk factors for SDH formation. Participants must have no prior history of SDH, as well as contributory procedures or medical history. Only nonelderly athletes are considered for the study.

Our secondary variables of interest that will be measured at baseline include age, sex, mechanism of neurological injury, and sporting category for multivariate analysis with logistic regression.

3.4: Statistical Methods

To test our primary hypothesis, we will be employing a chi squared test of independence with logistic regression for association. The variables will consist of hydration status,
dichotomously operationalized as dehydrated (BUN/Cr >20) or adequately hydrated (BUN/Cr < 20), and SDH presence which will also be dichotomous. Our null hypothesis is that SDH presence is statistically independent of hydration status, while our alternative hypothesis is that SDH presence is statistically dependent on hydration status – that is, dehydrated athletes will have greater odds of having an SDH. Further subgroup analysis will be conducted within the dehydrated group to see if the degree of dehydration relates to likelihood of SDH formation.

BUN/Cr values will be operationalized numerically against a dichotomous SDH outcome with a linear regression model. We intend to run multivariate analysis with logistic regression with the above secondary variables (age, sex, sporting category, and mechanism of SDH development) to account for certain confounders.

Pending sufficient data within patient charts, we intend to perform additional subgroup analyses within the group with SDH to test if dehydration affects condition severity. The severity of SDH will be measured by mean effusion size, GCS, and 30-day mortality. Mean effusion size will be operationalized numerically versus dichotomous hydration status with sample t-tests in a linear regression model. GCS will be expressed numerically versus dichotomous hydration status similarly with sample t-tests in a linear regression model. Finally, 30-day mortality from time of medical evaluation will be expressed dichotomously versus dichotomous hydration status; this will be done with chi square testing with logistic regression.

3.5: Data Collection

Data collection will exclusively be conducted through EMR review according to the Observational Medical Partnership (OMP) Common Data Model (CDM) \(^9\). Abstractors and coders of the data will be blinded to the hypothesis and intention of the study to decrease
reviewer bias, as well as trained with the standardized data abstraction manual to eliminate collection bias.

3.6: Sample Size Calculation

Although the exact incidence of SDH is unknown, acute subdurals are estimated to occur in 11% of mild to moderate head injuries that require hospitalization, and 20% of severe traumatic brain injuries\(^\text{10}\). Sports-related traumatic brain injuries occur at a rate of roughly 31.5 cases per 100,000 athletes\(^\text{11}\)– as such, we can estimate that acute SDH occurs at a rate of anywhere between 3.5 to 6.3 cases per 100,000 athletes. Chronic subdurals in adults younger than 59 occur at a rate of approximately 2.1 cases per 100,000 people\(^\text{12}\), with no known deviation when it comes to the athletic population. A rough estimate for total SDH formation in athletes is thus 5.6 to 8.4 cases per 100,000 athletes.

No study exists to date on the effect of hydration status on primary SDH formation risk. However, a reduction in brain volume occurs during dehydration\(^\text{13}\), while depressed brain volume may foster formation and reoccurrence of chronic SDH\(^\text{14}\). A cross sectional study by Mainka et al. additionally demonstrates that prehospital dehydration status is associated with increased likelihood of SDH reoccurrence (odds ratio: 10.3)\(^\text{14}\). Spontaneous intracranial hypotension, which may be secondary to acute dehydration\(^\text{15}\), is additionally associated with an increased incidence of SDH, with 26% of intracranial hypotension patients developing SDH\(^\text{16}\) (or 26,000 cases per 100,000 patients with intracranial hypotension– this includes severe dehydration, but with confounders such as neurovascular procedures). Finally, severe dehydration may impair sports performance and predispose athletes to injuries, including traumatic brain injuries\(^\text{17}\). Based on this relevant evidence, we anticipate a respectable effect size
of hydration status on SDH risk in athletes. However, we proceed with caution, as intracranial hypotension is not equivalent to a generalized dehydrated state.

The anticipated confidence level for our study will be 0.05, while our desired power will be 0.90. Our projected effect size is estimated to be 0.25993, based on the incidence rates of SDH in athletes and SDH rates in intracranial hypotension patients. A sample size calculation for odds ratios could not be conducted due to a paucity of existing data. To test our null hypothesis that the proportion of SDH occurrence differs between the control and exposure group, we will be conducting an uncorrected chi-square test. With the above parameters, the minimum sample size should be 33 per group. The sample size calculated falls under the assumption that there will be no missing data, and uses intracranial hypotension as a relative proxy for severe dehydration. Calculations were performed with Power and Sample Size Software version 3.1.6. See appendix for calculation.

In spite of our calculated sample size, we aim to retrieve all EMR patient records that meet our inclusion criteria in order to achieve the greatest possible power. After data collection and analysis is completed, a retrospective power calculation will be conducted using Power and Sample Size Software version 3.1.6.

3.7: Timeline and Resources:

The timeline of the study includes initiation in the Spring of 2023, with estimated completion of the study occurring within 2 years. Data collection consists of EMR review with no patient interaction or follow up, and will be conducted over a one-month period.

All study related activities will commence after IRB approval is granted, HIPAA authorization and Human Subject Protection Training has been completed by all personnel, and Waiver of All Consent or individual electronic consent has been granted. Staffing will consist of
a principal investigator, a statistician, and study personnel. The principal investigator will be a provider within the neurosurgical field, and will manage the integrity of the study design, prepare and manage the research grant, oversee all research activities, and conduct and report the research project. Study personnel will consist of a medical records specialist, who will be blinded to the study purpose and be tasked with perusing the EMR for pertinent data samples, as well as de-identifying and codifying data. The statistician will aid in review of the data, and conduct the delineated statistical analyses.

Funding needed for the study will comprise personnel salaries and the costs of pertinent data collection and analytical software. There will be no compensation for research subjects. According to the United States Bureau of Labor Statistics (USBLS), doctorate-level medical research scientists earn a median pay of $98,310/year, or $8,192.50/month. The USBLS also reports the median salary of a statistician to be $96,280/year, or $8,023.33/month. Finally, the median annual wage for a medical records specialist is $46,660/year, or $3,888.33/month. Our current technological needs are satisfied with OMP CDM open-source software, including the CDM R package, ARES, and ATLAS.

In summary, data collection for our study will occur over a one-month period, which will initiate in the Spring of 2023. Our staffing needs consist of a principal investigator, a study coordinator, study personnel, and a statistician. Funding for the study must include the costs of personnel salaries (estimated to be $20,104.16/month), and if need be, data collection instruments and analytical software.

**Figure 2.** Proposed timeline for research study.
3.8: Chapter 3 References


5. Ozbeki, Tina MD; Hamrick, Irene MD. What is the best way to identify dehydration in older adults?. Evidence-Based Practice 22(1):p 7-8, January 2019. | DOI: 10.1097/EBP.0000000000000199


Chapter 4 - Conclusion

4.1: Study Advantages

Advantages of this study include its novelty. While there are multitudes of case studies containing the exposure and outcome both in the general population and in our population of
interest, a correlation has yet to be statistically verified. We recognize that observational studies alone cannot constitute conclusive evidence.

Because of the retrospective study design, it is also affordable and requires no additional costs for recruitment or individual participation. Furthermore, the estimated time frame for the project requires less than two months for collection and analysis of data after IRB approval, as there is no direct patient contact required. As all data is collected at one time point and no patient care is involved, we anticipate no issues regarding missing primary variables or loss of follow up bias.

As the study includes all sites associated with the Yale New Haven Hospital acute care network, this will increase the generalizability and external validity of the study results. In conjunction with our plan to include all available EMR data within the past 30 years, as well as usage of a validated and common laboratory value for dehydration, our study design is more likely to procure a more robust sample size than previous published attempts.

4.2: Study Limitations

The retrospective nature of this study also poses a number of limitations. Most glaringly, we cannot establish the temporality between the exposure and outcome of interest, as both will have been detected within the same relative time period— it is impossible to determine if acute dehydration developed before or after the SDH did, or whether or not a transient hypohydration state had been correction prior to diagnosis. Because cases may have run as far as 30 years into the past, there are many external factors that may influence study results in ways unaccounted for by our multivariate analyses. For instance, there will be incorrigible information bias due to differences in data collection and practices across study centers. We must anticipate a degree of confounding and bias when conferring the results of the study to clinical practice.
Previous studies have also encountered scant sample sizes, although others have found success through the utilization of a retrospective cross sectional approach \(^1,^2\) which we will similarly be appropriating. Given the rare incidence of SDH in our population of interest, we anticipate a potentially small sample size (specifically within the exposure group) especially as we maintain rigid exclusion factors to minimize confounding. A major inclusion criterion requires study individuals to be athletes, which considerably further narrows down the population.

4.3: Clinical Significance

The results of our study will contribute to the existing body of research regarding the pathophysiology of SDH and risk factors regarding their formation especially within the context of young healthy individuals with no clear predisposition. Although there is proven physiological interplay between hydration status and intracranial protective factors against subdural hematomas \(^3\), the relationship between dehydration exposure and SDH formation risk has not been experientially proven to exist in athletes. We hope to elucidate a statistical correlation as it is currently unclear within the literature.

More importantly, we will be able to determine the neurological risks of transient dehydration on an athlete’s health, especially when analyzed with other variables such as sporting activity and direct head trauma. This information is valuable, as SDH are extremely catastrophic with high morbidity and long-term disability \(^4\), and dehydration may pose an easily modifiable and correctable risk factor. Results of this study may be used to inform guidelines regarding hydration repletion and safe weight cutting practices. Our research may also carry prognostic value within the clinical setting, as we are additionally examining the effect of dehydration on severity of SDH and its clinical presentation.
4.4: Chapter 4 References


Sample Size Calculation

Output

- Studies that are analyzed by chi-square or Fisher's exact test

- What do you want to know?
  - Sample size

- Case sample size for uncorrected chi-squared test
  - 33

Design

- Matched or Independent?
  - Independent

- Case control?
  - Case-Control

- How is the alternative hypothesis expressed?
  - Two proportions

- Uncorrected chi-square or Fisher's exact test?
  - Uncorrected chi-square test

Input

- \( \alpha \): 0.05
- \( p_0 \): 0.00007
- \( p_1 \): 0.26
- \( m \): 1

Description

We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the probability of exposure among controls is 0.00007. If the true probability of exposure among cases is 0.26, we will need to study 33 case patients and 33 control patients to be able to reject the null hypothesis that the exposure rates for case and controls are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.


62. Ozbeki, Tina MD; Hamrick, Irene MD. What is the best way to identify dehydration in older adults?. Evidence-Based Practice 22(1):p 7-8, January 2019. | DOI: 10.1097/EBP.0000000000000199


