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Prevalence of Thiamine Deficiency in Hospitalized Non-Alcoholic Veterans

NCT05480943

July 29, 2025

Title: Prevalence of Thiamine Deficiency in Hospitalized Non-Alcoholic Veterans

Principal Investigator: Dr. Elisabeth Mates, MD, PhD

Abbreviations:

ADL's	Activities of Daily Living
AIC	Acute Inflammatory Condition
CIC	Chronic Inflammatory Condition
COVID-19	Coronavirus Disease 2019
GI	Gastrointestinal
hs-CRP	Highly Sensitive C-reactive Protein
IADL's	Instrumental Activities of Daily Living
IV	Intravenous
MoCA	Montreal Cognitive Assessment
TD	Thiamine Deficiency
TDD's	Thiamine Deficiency Disorders
ThDP	Thiamine Diphosphate
WE	Wernicke's Encephalopathy

Revisions History: 8

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Background:

Thiamine deficiency (TD) causes a variety of thiamine deficiency disorders (TDDs) such as neuropsychiatric disturbances, polyneuropathy, ataxia, weakness and falling, and non-ischemic heart failure. Left untreated, TD can be associated with poor quality of life, loss of independence, and inability to complete activities of daily living. The prevalence of TD in non-alcohol using hospitalized Veterans is not known but is probably much higher than the general population which is thought to be less than 3%. Loss of functional ability leads to increased need for rehabilitation and consequent cost of healthcare. The objective of this proposal is to measure the prevalence of TDDs in Veterans who do not use excess alcohol who are ill enough to require hospitalization, determine if inflammation increases the risk of developing TD, and determine the optimal cutoff points for two biomarkers of TD to diagnose of TDDs.

The body's supply of thiamine depends entirely on dietary intake, there is no endogenous synthesis[1,2]. Thiamine is an essential cofactor for the metabolism of carbohydrates and amino acids[1,2]. Thiamine deficiency (TD) can develop quickly, within 18 days on a thiamine deficient diet or within 72 hours in critically ill patients[3]. Hospital inpatients are more likely to have micronutrient deficiencies[4]. COVID-19 infections may particularly increase the risk of TD because appetite, taste

and smell can be adversely affected. Neurologic complications in patients with COVID-19 are common in those requiring hospitalization[5], and thiamine responsive COVID-19 related encephalopathy has been described[6]. Thiamine deficiency disorders (TDDs) include conditions such as neuropsychiatric disturbances, polyneuropathy, ataxia, nausea and vomiting, weakness and falling, and non-ischemic heart failure.

TDDs are more common than currently appreciated in patients with specific medical conditions which often lead to hospitalization and subsequent rehabilitation needs. While TD and TDDs are reportedly less than 3% in high-income countries, there is a lack of generalizable prevalence, particularly in vulnerable populations such as the economically challenged, elderly, and chronically ill. Because symptoms of TDDs are often vague (fatigue, leg edema, imbalance, confusion, mood disorders, gastrointestinal (GI) upset, or muscle weakness) they are frequently attributed to comorbid diagnoses so under diagnosis among non-alcoholics is common[7]. Despite many published accounts of TD in acutely and chronically ill patients with conditions such as end stage renal disease[8], cancer[9], heart failure[10,11], dementia[12], acute psychiatric illness[13], stroke[14], diabetic ketoacidosis[15], critical illness[16], severe COVID-19 infections[6], and medically complicated obesity[17,18], there is a lack of appreciation for TDD diagnosis broadly, and specifically in Veterans. Acute Illnesses which increase metabolic demands can lead to TD more quickly including severe sepsis[3,16]. Elderly patients admitted to hospital seem particularly vulnerable[19–21]. Those who develop TDDs because of illness that leads to hospitalization will have more rehabilitation needs at discharge[22]. If TD is left untreated, the rehabilitation efforts will be less successful. If hospital providers were cognizant of increased risk of TDDs in their patients, it is more likely that thiamine replacement would occur leading to the best possible outcomes for patients and health systems alike. Based on a review of published accounts of TD in specific illness states, we estimate the prevalence in hospitalized patients could be as high as 25%[12,14,20,21,23–27]. The lack of basic prevalence data is an important knowledge gap that, left unanswered, will perpetuate the current state of under-diagnosis and under-treatment leading to persistent loss of function among at-risk Veterans.

We hypothesize that TD and TDDs are not rare in hospitalized Veterans who generally have higher chronic disease burden[28] and an incidence of malnutrition of 24% or more[29–31]. The etiologies of TD can be broadly categorized as insufficient intake (including malabsorption and toxin interference), increased need due to inflammatory stress (e.g. sepsis or active malignancy), and increased losses such as vomiting, diarrhea, dialysis[8] , or chronic diuretic use[10]. Hospitalized patients often have increased inflammatory stress due to acute and chronic forms of inflammation with concomitant cachexia[32,33]. Many use diuretics for hypertension and heart failure treatment. Most Veterans have poor intake leading up to admission from anorexia induced by acute and chronic illness and many suffer poverty and food insecurity with resultant malnutrition and micronutrient deficiencies[31].

TDDs often mimic other diseases and symptoms overlap with acute medical illnesses leading to missed opportunities for diagnosis and treatment. Many practitioners are unaware that TD occurs in non-alcohol using adults and the literature is full of case reports of near-miss diagnoses including mimics of Guillain-Barre syndrome[34,35], non-ischemic cardiomyopathy[36,37], refractory shock[38], worsening dementia[26], seizures[39], and acute psychosis[40]. In a stroke population admitted to acute inpatient rehabilitation, there was a 14% prevalence of TD with low plasma thiamine levels and an additional 49% with “low normal” levels, with over half of patients afflicted[14]. Thiamine is critical for brain function and as such, recovery from a stroke or other neurological insult requires at least adequate thiamine stores and perhaps higher than usual levels to meet rehabilitation goals. It is possible that acute illnesses resulting in prolonged debility requiring rehabilitation are in part due to TD, and that administration of thiamine may improve outcomes.

Case definitions of TDDs and evaluation of appropriate cutoff points of biomarkers are lacking. Many authors point out that the diagnosis of TD is a clinical one, not based on blood levels, although low blood levels are confirmatory[14,17,18]. TD should be defined as individuals with consistent clinical

symptoms AND either a low thiamine biomarker or significant improvement in or resolution of symptoms of TD after receiving thiamine supplementation[1,17,18]. Unfortunately, the available thiamine bioassays in the US (plasma thiamine or whole blood thiamine diphosphate (ThDP)) have reference ranges that are based on thiamine status in healthy individuals and have not been validated in those with clinical diagnoses of TDDs[1]. In addition, there is uncertainty in interpreting biomarker results and a lack of consensus on which biomarker is superior at distinguishing TD[41]. Experts suggest that whole blood ThDP normalized to RBC volume or hemoglobin concentrations should be used to ensure data from different studies are comparable[1]. Measuring serum and whole blood biomarkers concurrently would be important to validate each technique in the context of clinical TD that is responsive to replenishment. Filling the knowledge gap of clear case definitions of TDDs in non-alcohol using Veterans is an important step in achieving better outcomes with diagnosis and treatment.

Acute and chronic forms of inflammation may increase the risk of developing TD. It is accepted that inflammation is a significant risk factor for developing malnutrition[42,43]. Acute and chronic forms of inflammation are thought to contribute to the development of malnutrition through associated anorexia. Decreased caloric intake in combination with elevated resting energy expenditure (which increases the need for thiamine as a metabolic co-factor) leads to a downward spiral of depleting thiamine stores in the face of reduced oral intake. Concomitant measurement of inflammatory markers and thiamine biomarkers combined with clinical evaluation of TDDs is an open question, the answer to which is needed to further our understanding of this condition in Veterans and to develop potential mitigation strategies.

Study Aims/Objectives:

The **objective** of this proposal is to measure the prevalence of TD and TDDs in Veterans who don't use excessive alcohol and are ill enough to require hospitalization. Additionally, we will correlate biomarkers of thiamine with signs and symptoms of TDDs which improve with thiamine replenishment. Our central hypotheses are that the prevalence of TD in this population is as high as 25% based on reports of TD in various chronic disease states[3,12,14,19–21,24–26], and that TDDs reversible by replenishment may occur in the "low normal" range of blood thiamine levels[14,44]. The rationale underlying this proposal is that failing to define the prevalence of TD in this population will perpetuate the current state of underdiagnosing and undertreating TDDs which contributes to loss of independence and function. If our hypothesis is correct that the prevalence is as high as 25%, filling this knowledge gap will increase awareness of and bring action to address these problems through practice change and improved health outcomes. A parallel problem faced is that there are currently no commonly accepted clinically relevant cut-points for TD biomarkers available in the US. Clarifying the "abnormally low" biomarker cutoff levels by comparing TDDs with measured blood thiamine levels will fill a knowledge gap that has been identified[1]. Through carefully defining TDDs we will fill a critical knowledge gap and assist hospitalist and rehabilitation practitioners in making the diagnosis and implementing a treatment plan. Our **long-term goal** is to increase recognition and treatment of TDDs in Veterans by describing the clinical syndromes in non-alcoholics, as well as understand the root causes of TDDs. This will improve long-term health outcomes for Veterans with acute and chronic illnesses and help them maintain independence and function. We will test our central hypothesis and attain our objectives via the following **specific aims**:

Aim 1: Utilizing a prospective cohort study design, determine the prevalence of TD, as defined by whole blood and plasma thiamine levels and symptom responsive disease, and describe social and medical factors predisposing to TD in consecutively hospitalized non-alcoholic medicine patients. Hypothesis 1: The prevalence of TD in hospitalized Veterans who do not use excessive alcohol is between 10 and 25%, much higher than the general population estimate of less than 3%.

Aim 2: Through an open label treatment study, we will define thiamine deficiency disorders (TDDs) as cases with low or "low normal" thiamine levels and symptoms of TD that improve with thiamine replenishment. Hypothesis 2: The current bioassays of thiamine do not accurately define TDDs and individuals with results the "low normal" range will show symptom improvement with thiamine replacement.

Aim 3: **Utilizing a nested case control study design, determine if acute and chronic inflammatory conditions with elevated biomarkers of inflammation increase the risk of developing TDDs.** Hypothesis 3: Acute and chronic forms of inflammation cause oxidative stress which increase basal requirements for thiamine as a metabolic cofactor and increase the risk of developing TDDs.

Study Population:
We anticipate 300 patients will be enrolled in this study with an age range of 18 and older. There will be no exclusions due to gender, race, age, or ethnicity. We will endeavor to include women and minorities to the extent possible based on the inpatient population which historically has been predominantly male (95%) and white (90%). All subjects recruited for this study will be Veterans admitted to inpatient units at VA Sierra Nevada Healthcare System hospital (single site recruitment). There will be no minor children participating. The health status will be compromised from mild to severe due to the nature of being hospitalized. We will not include adults unable to consent (those who are cognitively impaired with Impaired Decision-Making Capacity). We will not enroll pregnant women as we do not admit them to the VA hospital due to lack of maternity services.

Inclusion criteria:

- anyone age 18 or older requiring full hospital admission to the medical service.

Exclusion criteria:

- excess alcohol intake as defined by the National Institute of Alcohol Abuse and Alcoholism as more than 14 standard drinks per week for men less than age 65, or more than 7 drinks per week for women or men 65 years of age or older
- unable to consent due to impaired decision making capacity.
- veterans who live more than 75 miles from the study site as that would likely hinder their ability to attend follow up visit 3.
- Veterans who suffer from quadriplegia because they cannot participate in the physical assessments
- Veterans taking thiamine supplements

Vulnerable Populations:
The population enrolled may include vulnerable populations such as those with memory loss or neuropsychiatric symptoms that may be a result of thiamine deficiency. Through this research we hope to find potential treatments for these conditions which are disabling. We will assess their decision-making capacity during the consent process utilizing the U-ARE Protocol[45].

Sample Size:
Current best estimates for TD in similar populations are approximately 25%[19,24,27]. Such an enrollment would provide us with a precision of TDD prevalence of +/- 5.4%. A sample size of 300 and estimated drop out of 15% leaving 255 subjects would provide us with 81% power to detect an 8% absolute difference from this expected prevalence.

Recruitment Process:
We will apply for a HIPAA waiver to preliminarily review charts of newly admitted Veterans for eligibility. Each workday, we will obtain a list of veterans newly admitted to the hospital from administration since the previous workday (on the first workday of a week, this will include weekend admissions). We will not use advertising to recruit potential participants. For those who do not have exclusion criteria, we will approach the patient to discuss the study and determine if they have capacity to consent to the study. If they lack capacity at the time we approach them, we will discuss with the treatment team whether the lack of capacity is expected to be temporary, due to their acute medical condition, or permanent due to underlying neuropsychiatric disease. If it is deemed temporary, we will approach the patient later in the hospital stay when their acute conditions have

been treated and discuss the study again to see if their capacity has improved to a degree where informed consent is possible.

Screening Procedures:
The research coordinator will preliminarily review charts for exclusion criteria.

Informed Consent Process:
To obtain consent the research coordinator will approach the Veteran in their hospital room and ask if they wish to hear about the research we are conducting. If they are willing, they will describe, in plain English, the health effects of thiamine deficiency and the current knowledge deficit of what percentage of hospitalized Veterans suffer from it. We will confirm capacity utilizing the format of the U-ARE protocol[45]. We will emphasize that participation is wholly voluntary and that they may stop participating at any time without penalty. We will discuss the fact that this research is designed to measure how often hospitalized Veterans suffer from thiamine deficiency which may result in the improvement of diagnosis and treatment of this condition in the Veteran population. We will describe the study procedures which will include several interviews by study staff, extra blood work which will be timed to coincide with routine blood work where possible, targeted physical examination, possible prescription of thiamine replacement. Lastly there may be a single follow up visit after treatment which will include interview, physical exam, and repeat blood draw. The total duration of participation will be four weeks or less. We will describe the fact that Veterans whom we suspect have TD based on their symptoms and/or physical exam will be prescribed oral thiamine replenishment and followed for symptom improvement. There will be no blinding of participants so that if thiamine is prescribed, they can be assured they are provided the vitamin and not a placebo. We will describe the possible risks of bleeding or bruising from phlebotomy. We will discuss the potential outcomes if the deficiency is left untreated such as worsening memory, weakness, falling, difficulties with eyesight, heart failure, nerve damage and in extreme cases death. There are no alternative treatments for TD besides vitamin replacement. If during participation in the study, we discover other vitamin or nutritional deficiencies, we will notify the patient's primary care provider to address these deficiencies. There will be no genetic material collected or stored because of this study. The consent form will also provide all participants with the principal investigator's and study coordinator's contact information to answer any questions that arise later.

Data Collection Procedures:

10 STUDY INTERVENTIONS

Table 3: Study procedure schedule of evaluations

	Visit 1- early hospitalization	Visit 2 – late hospitalization	Visit 3 – after 2 weeks of thiamine repletion
Chart review for social and medical histories	X		
Symptom and function survey		X	X
Targeted physical exam		X	X
Nutritional history		X	
Lab draw for thiamine biomarkers	X		X
Blood draw for prealbumin , others as needed	X		
Thiamine repletion	X[1]	X[2]	

1. For select patients with WE or severe symptoms of thiamine deficiency 2. all others

10.1 Visit 1 – initial hospital encounter: The Veteran's chart will be reviewed for acute and chronic medical problems, habits, and social history. We will schedule lab testing (as described below) to coincide with routine morning blood draw to avoid additional phlebotomy. For those who present with symptoms of Wernicke's encephalopathy (WE) which requires urgent parenteral thiamine replacement, we will perform our history and exam promptly and advise the primary inpatient treatment team to initiate therapy if they meet the Caine criteria[46] for WE. For all others who do not have evidence of WE, we will proceed to visit 2.

Thiamine biomarker and other micronutrient assessment: Fasting plasma thiamine levels and whole blood ThDP will be ordered for collection by lab personnel as soon as feasible after consent is obtained from the Veteran. We will also order blood levels of vitamins B12, D, and folic acid as well as prealbumin if not done via routine care within the preceding four weeks. In addition, we will extract albumin, complete blood count, and magnesium as ordered by the primary team as part of routine care There will be no genomic sequencing, in whole or in part, as part of this analysis. Blood specimen will be collected as part of routine medical care by laboratory personnel. Lab tests not routinely run in our local laboratory will be sent out to reference labs per the usual practice of the Department of Pathology. There will be no direct handling of blood specimen by the research team. Results of the lab tests will be available in a participant's electronic medical record and will be extracted by the study coordinator and stored in a de-identified database. If they have been prescribed thiamine replenishment and the thiamine lab values are lost, we will include the remaining data gathered in the study.

10.2 Visit 2 – second hospital encounter: Following stabilization of the acute medical condition(s) for which they presented, the Veteran (and caregiver if the Veteran agrees) will be interviewed and examined by the study's PI or trained advance care practitioner using a standardized checklist of signs and symptoms of TD. We will delay this portion of the assessment until the primary treating team affirms their acute condition has stabilized to avoid misclassification of symptoms from the acute illness with those of TDD. In most cases we anticipate this will occur just prior to hospital discharge. For Veterans with symptoms suggestive of TD, we will provide a prescription for thiamine replacement 100 mg orally daily for two weeks (see **Standardized physical examination and related data**).

Nutritional history: Study personnel will perform a dietary history to adequacy of thiamine intake, recent changes in appetite, food intake or any social or medical risk factors for malnutrition. We will review medical records for acute and chronic medical illnesses that may predispose to malnutrition.

Symptom and function survey: The patient interviews will include questions about the following: acute or worsening symptoms in the following categories: neuropsychiatric (including memory loss, personality or behavior change, psychosis, mood changes, seizures), polyneuropathy (to include muscle weakness, loss of deep tendon reflexes, neuropathic pain, or sensory loss), GI dysfunction (including dysphagia, anorexia, nausea, vomiting, gastroparesis, or constipation), and cardiovascular manifestations (such as palpitations, tachycardia, dyspnea, pulmonary or peripheral edema). We will review recent trends in ability to carry out Basic Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs). We will determine if there are symptoms of adult failure to thrive such as weight loss, decreased appetite, inactivity, poor nutrition, depression, loss of functional status as defined by loss of ability to do ADLs or IADLs. We will also ask about medication compliance with both prescribed and over the counter medications and supplements.

Standardized physical examination and related data: We will perform targeted exams for signs of TDDs including mental status exam using the Montreal Cognitive Assessment (MoCA); delirium screen using the 4AT

clinical test; ophthalmoplegia and nystagmus using the “H” test; evaluations of ataxia, peripheral neuropathy, deep tendon reflexes, and muscle strength using the Medical Research Counsel Adaptation B scale. We will assess for signs of cardiovascular dysfunction such as pulmonary or peripheral edema and tachycardia, and GI signs such as decreased bowel tones. We will assess physical signs of malnutrition including muscle and fat loss and trends in body weight. We will review any existing radiologic studies for evidence of abnormal brain imaging, echocardiogram results, pulmonary edema, or ileus for example.
For patients with severe symptoms such as inability to ambulate, or WE, we will advise the primary treatment team to begin high dose intravenous (IV) thiamine replenishment at 400 mg every eight hours for nine doses while inpatient. In this group we will then prescribe oral thiamine 100 mg once a day after IV therapy is complete until visit 3. For patients with mild-moderate symptoms that could be due to TD, the research pharmacist will process and dispense oral thiamine 100 mg once daily at hospital discharge. If the patient is discharged when the research pharmacist is not at the hospital, the research pharmacist will mail it to the patient on the next business day. Patients who are discharged to skilled nursing facilities, or any other rehabilitation facility, will be contacted by the research team and be medically advised to supplement the patient with oral thiamine 100 mg. We anticipate return of lab biomarker results 7-10 days after they are drawn at which point any individual not identified by clinical screening to have TD will be contacted and oral replenishment initiated. As with the symptom and function survey we will record these findings on a government furnished computer with a paper record as backup.

10.3 Visit 3 – follow-up of symptomatic Veterans after empiric thiamine treatment. All Veterans with low biomarkers OR low normal biomarkers and clinical symptoms of TDDs that were initiated on replacement will be seen at a follow-up visit 3 after two weeks of thiamine replacement. We will repeat the symptom and function survey and repeat the standardized physical assessment. We will categorize changes in symptoms and signs as *no or minimal improvement, or noticeable improvement*. We will re-order thiamine biomarkers to assess for increases in levels. We will recommend continued dosing with thiamine 100 mg daily thereafter for any Veteran with improvement in their symptoms and update their medical record to include thiamine deficiency in their problem list. If a participant failed to complete the 2 weeks of replenishment, we will provide another 2-week course of replenishment and reschedule this visit.

Study Duration/ Study Timeline:
See Table 3. We expect visit 1 will not take substantial time for the Veteran. Visits 2 and 3 will take between 60 and 90 minutes each. For Veterans without symptoms of TD, their participation will be complete after visit 2, before discharge from the hospital. For Veterans with symptoms of TD their participation will be complete after taking thiamine for 2 weeks and attending visit 3. We anticipate the study will end 24 months.

Study Endpoints:
Our primary endpoint will be determining prevalence of TD in our Veteran population. We do not anticipate stopping the study before 300 Veterans are recruited. Thiamine supplements are very safe with few side effects, so we do not anticipate stopping early for safety concerns.

Study Locations:
The study will be conducted at the VA Sierra Nevada Healthcare System Hospital inpatient units at 975 Kirman Avenue, Reno, NV. Follow up visits will occur on the ground floor of the hospital in the research department exam rooms.

International Research:
We will not be conducting this research in international locations.

Participant Compensation:
Those that agree to participate will be compensated $30 for visits 1 and 2 and $200 if they attend visit 3 after discharge.

Economic Burden to Participants:
Veterans will not incur any costs because of participating in this study. Those that attend the follow up visit will incur the cost of transportation, but this will be mitigated by the $200 compensation.

Risk to Participants:

The principal risks to the patient are those associated with phlebotomy, namely discomfort and bruising associated with a needle stick. All efforts will be made to combine our tests with routine phlebotomy draws ordered by the primary treatment team. In some cases, additional time spent with investigators performing interviews and physical exams may cause psychological distress. In cases where thiamine is prescribed to treat suspected thiamine deficiency, there are rare instances of adverse reaction to parenteral thiamine such as anaphylaxis, pruritis, and local inflammation. Oral thiamine is typically well tolerated, the main difficulty is possibly having trouble swallowing tablets. There are extremely rare instances of side effects such as flushing, hives, itching, weakness, sweating, nausea and restlessness.

Protection Against Risk: The risk of bleeding or bruising due to phlebotomy will be mitigated by combining our specimen collection with routine collections placed by the primary treatment team to avoid extra phlebotomy. Only qualified personnel will draw blood. For psychological stress suffered, the Veterans will be assured they may refuse and withdraw from the study at any time if it becomes too burdensome. For instances where parenteral thiamine is ordered, it will be in a hospital setting where prompt medical attention is available should anaphylaxis or other side effects occur. For Veterans prescribed oral thiamine replacement who have difficulty swallowing tablets, a pill crusher will be provided. Any adverse reactions to parenteral or oral thiamine repletion will be recorded and replenishment discontinued.

Confidentiality Risks: Every effort will be made to keep all research information obtained from blood samples confidential, but absolute confidentiality cannot be guaranteed. Laboratory data obtained from blood samples will appear in the medical record for review by VA medical providers. The research information obtained as a result of participation in this study will be included in the medical record and may be given to primary care doctors. Information from which participants may be personally identified will be maintained in a confidential, locked file and will not be disclosed to third parties except with participant permission or as may be required by law.

A progress note will be included in the patient's medical record for all research subjects who receive research procedures or interventions as inpatients or outpatients at VA medical facilities that are either used in or may impact the medical care of the research subject at a VA medical facility or at facilities VHA Directive 1200.05(2); 1/7/2019.

Benefits to Participants:
The potential benefits of research to subjects and others include improvement in thiamine deficiency symptoms where thiamine replenishment is prescribed. Other potential benefits include improved health outcomes for all Veterans by increasing awareness of the scope of the problem of thiamine deficiency in those hospitalized and mitigation of this health problem. Thiamine deficiency is currently thought to be rare in the United States in people who do not drink excess alcohol. However, there is evidence that demonstrates it is not rare and is often overlooked as a cause of weakness, falling, memory loss and other problems that cause debility. The results of this study will help us understand the magnitude of the problem in vulnerable Veterans who are ill enough to be hospitalized. We anticipate this knowledge will increase awareness of thiamine deficiency as a problem for hospitalized adults and treatment will improve quality of life for Veterans.

Privacy of Participants:
We will apply for a HIPAA waiver to initially review a potential Veteran participant's chart for exclusion criteria. This will be a very limited chart review. Once eligibility is determined, the Veteran will be approached his/her private or semi-private hospital room. If the Veteran is in a semiprivate room and requests the study interview and exam occur in a private room, every effort will be made to move them to a private room for the study procedure.

Data Management and Confidentiality:
All participants will be assigned a unique ID upon their initial screening appointment. The unique ID will be randomly generated to ensure no identifying information is used to reference participants throughout the course of the study. A linking database will then be established by the PI using excel that will allow for the investigator to re-identify subjects if the need arises (Serious Adverse Events (SAE), Unanticipated Problems (UP), etc.). Only the PI and delegated members as of the research team will have access to the linking database which will be password protected and remain on the VA premises at all times. All data collected and stored in the repository will be coded using unique IDs to ensure the identify of subjects cannot be readily ascertained. Only RDC/IRB approved members of the study team will have access to the data repository which will be password protected and stored within the VASNHCS servers on the VHA network.

Data for this study will be used for research purposes only, stored securely within the VA. In the event of an accidental disclosure or breach of personally identifiable information (PII), the facility privacy officer will be notified as soon as the PI is aware of the issue. All telephone conversations involving PII will be led by IRB-approved research staff and conducted in private confidential spaces either within a VA office or at an approved teleworking location. A deidentified dataset will be created to be shared with former VA research staff member who is now a community member without VA affiliation due to external circumstances. She wishes to continue assisting with data analysis when needed. De-identified data which may be shared with non-VA staff will be stripped of all Protected Health Information (PHI), including all 18 HIPAA PHI identifiers, per the Safe Harbor standard of de-identification under HIPAA. De-identified data may be sent electronically through IRBnet.org or VAIRRS to IRB-approved staff for safety and protocol deviation reporting. All data will be stored and maintained in accordance with VHA Records Control Schedule (RCS) 10-1. Deidentified group or aggregate data will be reported in research publications or at scientific conferences following privacy officer approval; however, no identifiable data will be included. Identifiers will be removed from the data and after such removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative. No biospecimen will be retained or distributed to other researchers. While this study will store de-identified data for future research, the use of this data will not affect the rights or privacy of participants. The research team will ensure privacy and confidentially of all participants is maintained throughout the study.

Any data recorded on paper will be stored in a locked file cabinet inside the locked research offices at the VA.

Provisions to Monitor the Data to Ensure the Safety of Participants

Thiamine repletion is considered very safe with extremely rare side effects (less than 1%) as such we do not anticipate and serious adverse events. Side effects of intravenous thiamine are reported to be flushing, restlessness, sweating, itching, hives, nausea, gastrointestinal bleeding, anaphylaxis, angioedema, weakness, and pulmonary edema. Oral thiamine (the formulation used in this study) may have similar side effects although far less commonly than the rare effects noted with IV thiamine. Thiamine is an approved treatment for Wernicke's encephalopathy and has been used widely in medical practice since the 1950's. We will not be using any new formulations or doses outside of current recommendations for the treatment of symptoms of thiamine deficiency. The PI, study coordinator, and Health Systems Specialist will monitor Veterans prescribed thiamine repletion and report any new or unusual symptoms to the IRB.

Data and Specimen Banking
During screening and recruitment, data will be on paper and stored in the research department in a locked cabinet behind locked department doors, building 1 room C3334. Only the PI and study personnel will have access to these records. Once a veteran agrees to participate and is enrolled in the trial, all subsequent data will be stored electronically on the restricted research drive. For veterans who are screened but not enrolled, their records will be maintained for 7 years in accordance with VHA Records Control Schedule (RCS 10-1). All study data will be stored both on paper in locked filing cabinets and electronically in the data collection tool REDCap. We will not be storing any specimen.

Data will be stored electronically in \\r01renhsm01.r01.med.va.gov\research\Principal Investigators\Elisabeth Mates\Thiamine Research and in REDCap (varedcap.rcp.vaec.va.gov). Data that will be stored electronically include:

1. Unique study ID number with patient name and last 4 of social security number and telephone number in a master key spreadsheet, to be separated from the remainder of the data.
2. Remainder of data stored in the database include the unique study ID, age, sex, race, ethnicity, all lab results (as described in Procedures section 10.1), nutrition screening results (as described in Procedures section 10.2), symptom and function survey (section 10.2) and physical exam findings (section 10.2). For symptomatic veterans who are started on thiamine repletion, the symptom and function survey and physical exam findings will be repeated at visit 3 and recorded in the database.

Paper records of data include:

1. Patient name and hospital room number.
2. All study data will be recorded on paper and stored in locked file cabinets within the locked research department.

Sharing of Results with Participants
Thiamine and other micronutrient results will be shared with Veteran participants and will be available for them to view in their electronic medical record. For Veterans found to have low thiamine levels, we will call the veteran and start them on thiamine tablets if they haven't already been started on them. We will notify their primary care doctor as well to ensure ongoing thiamine repletion after the study has concluded.

Withdrawal of Participants
We do not anticipate withdrawing participants from our study without their consent. Participants may withdraw from the study voluntarily at any time by in person meeting or telephone contact with study managers. The Principal Investigator also reserves the ability to early exit subjects from the study at any time in the event a subject is non-compliant with study visits any other component of the study. This will be exercised at the digression of the PI only after multiple contact attempts have been made and a certified letter sent to the subject.

Approach to Analysis:
All data will be analyzed by a statistician affiliated with the VA research department trained biostatistician. The data will be analyzed using the statistical software SAS on the VA Informatics and Computing Infrastructure (VINCI).

15.1 Prospective cohort study to determine the prevalence and risk associations of TD.

Measurements: The **primary outcome** of this study is to measure the prevalence of TD as defined by abnormally low or low normal thiamine biomarkers combined with symptoms that respond to thiamine replenishment. **Secondary outcomes** will include describing demographic, clinical, and nutritional characteristics among those with and without TDDs. A TDD will be defined as an acute condition with symptoms that are known to be due to TD and that improve with adequate thiamine replenishment.

Statistical analysis/power calculations: Our primary endpoint is the prevalence of TDDs which we will compute as the proportion of TDD cases over the total number of subjects enrolled. Given the feasibility of this study and our patient population, we believe we can enroll and follow 300 subjects over a one-year enrollment period with an anticipated drop-out rate of 15%. Current best estimates for TD in similar populations are approximately 25%[19,24,27]. Such an enrollment would provide us with a precision of TDD prevalence of +/- 5.4%. A sample size of 300 and estimated drop out of 15% leaving 255 subjects would provide us with 81% power to detect an 8% absolute difference from this expected prevalence. To explore differences in demographic, clinical, and nutritional characteristics among those with and without TDDs, continuous variables will be compared by T-test unless parametric assumptions are not met in which case a Kruskall-Wallis test will be used. Categorical variables will be evaluated through Chi-square or Fishers exact test depending on assumptions being met. We will estimate prevalence rate ratios for association factors. If the prevalence is achieved, we estimate that we would have adequate numbers to identify a range of different rates of exposure variables among TDD and non-TDD patients. For example, with 63 TDD and 192 non-TDD patients and a 10% rate of a given explanatory variable, we would have 80% power to detect prevalence rate ratios of ~2.5 and higher in bivariate analyses.

15.2 Open label treatment study to develop standardized case definitions of treatment responsive TDDs and correlate with thiamine biomarker levels to determine clinically relevant cut-points of those biomarkers.

Measurements: The **primary outcome** of this arm is to describe the prevalence of treatment responsive TDD symptoms in the hospitalized Veteran population. The **secondary outcome** is to explore cut-points of thiamine biomarkers that can be utilized to diagnose TDDs with more sensitivity than current clinical laboratory limits.

Statistical analysis: Descriptive features of treatment responsive TDD patients will include frequencies of symptoms, physical exam findings, and functional disability compared to patients without TDDs. We will describe each case's initial signs and symptoms and improvements. To better define the thiamine levels that differentiate thiamine responsive from thiamine non-responsive symptoms, the levels of thiamine will be compared between groups using Kruskal–Wallis test corrected for multiple comparisons. For the two thiamine biomarkers, the optimal cut-point to distinguish between thiamine responsive and thiamine non-responsive symptoms will be determined by applying the Liu method[47] to maximize the product of the sensitivity and specificity. Based on the cut-points, thiamine levels will be dichotomized into lower and higher or equal to the cut-point and the area under the receiver-operating curve (AUC), the sensitivity, specificity, positive and negative predictive values, and the likelihood ratio will be computed. These cut-points will be compared to that of the current laboratory reported abnormal cut-points. For this aim the power to identify discriminating cut-points will be dependent up on the prevalence of the treatment responsive disorder and the distribution of thiamine levels. Under conservative assumptions (alpha 0.05, beta 0.80) and a 2 to 1 ratio of negative responders to positive responders at a given thiamine cut-point level, we would need 19 responders and 38 non-responders for a given symptom to estimate an area under the curve (AUC) of 0.725 compared to a null AUC of 0.50. While there is no information to inform the reasonableness of these parameters, we believe we will have reasonable ability to explore thiamine level cut-points for treatment responsive TDD for this exploratory aim.

4.3 Nested case-control study to determine if inflammation is associated with the presence of TD in hospitalized veterans.

Measurements: The **primary outcome** of this arm is to determine if there are differences in markers of inflammation as evidenced by hs-CRP and fibrinogen between TDD and non-TDD hospitalized Veterans. Presence of inflammation will be defined as hs-CRP higher than upper limits of normal 0.75 milligrams/deciliter (mg/dL), or fibrinogen higher than the upper limits of normal 471 mg/dL. Individuals will also be considered to have inflammation if they are diagnosed with one of the AICs or CICs previously described.

Statistical analysis: The presence or absence of AICs and CICs among those with and without TD (defined as treatment responsive TD or abnormal thiamine levels based on clinical laboratory standards) will be evaluated by Chi-square or Fisher's exact test depending on assumptions being met. An assessment of total number of AICs and/or CICs between TD and non-TD patients will be assessed using the student's T-test or non-parametric methods depending on necessary assumptions being met. To evaluate if biomarkers of inflammation (hs-CRP and/or fibrinogen) are associated with presence or absence of TD we will compare levels between these two groups. If group sizes are large enough, we will attempt to develop exploratory multivariate models to identify AICs, CICs, and inflammation markers which are associated with TDD status. As no studies have reported on inflammatory markers, AICs, and CICs and thiamine deficiency, this is an exploratory aim for which we have no data to estimate a priori sample size requirements.

Resources Available

The VA hospital is a 64-bed general medical and surgical facility. There are typically 10 patients admitted to the hospital daily and we expect no trouble enrolling 300 patients in our study over 12 months. Dr. Mates will dedicate 3/8ths of her full-time employment with the VA managing this project. We will have a full-time research coordinator and a half time Health Systems Specialist (PA or ARNP) performing the day-to-day operations of the study. Dr. Mates will train both employees on the research purpose and protocol and assign duties as appropriate to their background and training in completion of the study. Veteran participants will be given a detailed description of their role in the research project and will be provided phone numbers to contact study personnel in the event of an adverse outcome or symptom. All medical and psychological care will be provided through the VA for adverse events.

Mentorship Plan for Medical Trainees Conducting Research

NA

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