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PRINCIPAL INVESTIGATOR: Dr. Ellen Mackenzie

CONTRACTING ORGANIZATION: JOHNS HOPKINS UNIVERSITY
Baltimore, MD 21218

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6. AUTHOR(S)
Ellen J. MacKenzie, PhD

E-Mail: emacken1@jhu.edu

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METRC Coordinating Center
Johns Hopkins Bloomberg School of Public Health
415 North Washington Street
Room 363
Baltimore, Maryland 21231

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14. ABSTRACT
Background. The Military Extremity Trauma and Amputation/Limb Salvage (METALS I) Study examined differences in outcomes among individuals with major limb trauma undergoing amputation or limb salvage deployed to Afghanistan or Iraq between 2003-2007 who sustained major limb trauma to the upper and/or lower limbs resulting in amputation or limb salvage. Results from interviews and medical record abstraction (n=429) showed that major limb trauma leads to significant physical and psychosocial disability, and that outcomes among those who underwent limb salvage were significantly worse than those who underwent amputation. **Objective/Hypothesis.** (1) examine long term function outcomes for METALS 1 participants; (2) compare early outcomes for the METALS I participants to a new cohorts (METALS 2) injured between 2008-2013; (3) examine incidence of short and long term complications; and (4) examine short and long term use of medical, mental health and rehabilitation services. **Study Design:** Retrospective cohort study of eligible individuals in the original M1 cohort (N=995) and individuals injured between 2008 and 2013 (N=544). **Principal sources of data:** (1) an interview at 7-10 (M1) or 2-3 (M2) years post-injury and (2) claims data from the DoD and Veterans Health Administration **Key Findings:** Major limb trauma sustained in the military leads to significant physical and psychosocial disability. While individuals in M1 who underwent limb salvage were initially doing better than those who underwent amputation, an average of 13 years later, these differences were essentially erased, and there were no differences in function between the groups. Participants in M2 were more likely to undergo limb salvage than those in M1, but were, on average, more likely than those in M1 to suffer from depression, anxiety, PTSD or substance use disorders in the early years following their injuries. Overall, across the two cohorts, we found short and long term complications to be similar between amputees and limb salvage patients in the 5 years following injury, although amputees were more likely to experience cardiac conditions and infection complications. Finally, the M2 cohort had overall higher healthcare utilization in the 5 years following injury, but that these rates did not vary by limb salvage status.

15. SUBJECT TERMS
Outcomes, amputation, limb salvage, major limb trauma in the military

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Table of Contents

Military Extremity Trauma Amputation/Limb Salvage (METALS) Study: Long-Term Follow-Up

Dr. Ellen J. MacKenzie
Dr. Jessica Rivera
Dr. MaryJo Pugh

Final Report
December 2022

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Executive Summary

The Military Extremity Trauma and Amputation/Limb Salvage (METALS I) Study examined these differences using a retrospective cohort study of service members deployed to Afghanistan or Iraq between 2003-2007 who sustained major limb trauma to the upper and/or lower limbs resulting in amputation or limb salvage. Results from interviews and medical record abstraction (n=429) showed that major limb trauma leads to significant physical and psychosocial disability, and that patients with lower limb trauma who underwent amputation experienced significantly better outcomes than those undergoing limb salvage. Since this cohort was studied, changes to the military's treatment and rehabilitation protocols were hypothesized to have improved outcomes for both groups and reduced differences in outcomes between amputees and limb salvage patients. The purpose of the METALS 2 study was to follow up with METALS 1 cohort and assess long term outcomes, and to enroll a new cohort of servicemembers injured between 2008 and 2013.

A total of 1,007 potentially eligible participants were identified (424 from M1, 580 from M2). Among these participants, no contact data were available for 188 (M1: 64, M2: 124), for a total denominator of 819 attempts. Although the unadjusted response rate was 61% (M1: 67%, M2 56%), among the 819 participants with available contact information, 612 interviews were completed (74.7%) (M1: 286/360 (79.4%); M2: 326/456 (71.5%)).

Products from this study are varied. The study abstractors were responsible for ensuring the entry of detailed injury and treatment information on all consented METALS 2 participants into the Military Orthopaedic Trauma Registry maintained by the Joint Trauma System, ensuring that these data will be available for future research purposes. The investigators will ensure analytic access to the rich, deidentified, merged dataset created as a part of this study, which includes interview data and time 1 and time 2 for the METALS 1 cohort, interview data for the METALS 2 cohort, and all Veterans Health Administration utilization data for 10 years following injury. These data are available upon presentation and approval of an analytic plan to the Major Extremity Trauma Research Consortium (METRC) publications committee. Analysis for all four aims of the study was completed, and results are presented in this report. While final write up and publication is pending, results have been disseminated in several important ways. In 2018, a poster was presented at the MHSRS meeting, summarizing the potential impact of selection bias in this population, "Selection Bias in Military Cohort Studies: An Analysis of Differences between Participants and Non-Participants in a Study of Service Members with Severe Limb Trauma." Key dissemination activities are planned for the coming year. Two abstracts were accepted for podium presentation at the 2023, "Changes in Functional Outcomes Over Time Following Major Lower Limb Trauma Among Veterans Undergoing Primary Amputation versus Limb Salvage" and "Changes in Functional Outcomes Over Time Following Major Lower Limb Trauma Among Veterans Undergoing Primary Amputation versus Limb Salvage," and the same two abstracts were accepted as posters at the MHSRS 2023 meeting.

1. Introduction:

Although major limb trauma resulting from combat operations in Iraq and Afghanistan is common, little is known about how treatment of these injuries impacts outcomes (1-2), leaving clinicians with little data to guide decisions in the acute and post-acute care settings. Of particular interest are differences in outcome following amputation vs. reconstruction of the most severely injured limbs (3). Since 1987 when Dr. Sigvard Hansen (4) published a plea for the development of treatment guidelines to avoid "… prolonged, costly and fruitless salvage procedures" several investigations have compared outcomes under amputation vs. limb salvage. Most of this literature has been based on the experience of civilian level I trauma centers (5-10). However, more recent investigations in the military (11-15) are informing the results of these civilian studies. The Military Extremity Trauma and Amputation/Limb Salvage (METALS I) Study examined these differences using a retrospective cohort study of service members deployed to Afghanistan or Iraq between 2003-2007 who sustained major limb trauma to the upper and/or lower limbs resulting in amputation or limb salvage. Results from interviews and medical record abstraction (n=429) showed that major limb trauma leads to significant physical and psychosocial disability. In addition to impairments in the Mobility and Hand/Arm domains of the Short Musculoskeletal Function Assessment (SMFA), percentages of participants with positive screens for depression (38%) and PTSD (19%) were greater than U.S. population norms.(11-13) Furthermore, increased rates of pain, depression, and PTSD were shown to be linked to poor functional outcomes a year following injury (12).

Disability was prevalent among both amputees and limb salvage participants in METALS I. However, patients with lower limb trauma who underwent amputation experienced significantly better outcomes than those undergoing limb salvage.(11) These results stand in contrast to those of the civilian Lower Extremity Assessment Project (LEAP), a prospective study of 545 adults with leg injuries similar to those studied in METALS.(9, 10) After adjusting for differences in patient and injury characteristics, the LEAP study found no differences in outcomes following amputation vs. limb salvage as measured using the Sickness Impact Profile (SIP).(16) As with the METALS study, however, outcomes were generally poor across both groups; only 51% returned to work at 2 years and 42% screened positive for depression and/or anxiety.(17, 18)

Differences in the METALS and LEAP study results may be due to greater access to state-of-the art prostheses and prosthetic care for Military vs. civilian amputees.(19-21) In addition, amputees in the Military may have benefitted from more focused rehabilitation and support services compared to both Military limb salvage patients and civilian amputees. Rehabilitation protocols for amputees, including an emphasis on peer support, have been well established through the Military Amputee Care Programs.(22, 23) Treatment pathways and support services for limb salvage patients have been less well defined given the wider spectrum of injuries and treatment courses. A study of TRICARE claims(14) showed that compared to lower limb amputees, limb salvage patients (injured 2003-2007) received less outpatient care in the first 2 years, especially for psychological problems with 88% vs. 29% of amputees and limb salvage patients, respectively, receiving psychiatry appointments. However, in the years since the original METALS study was recruited, increased focus on "Amputee and Limb Salvage" clinics instead of "Amputee" clinics and development of technology and rehab protocols targeted at limb salvage recovery (e.g. the Intrepid Dynamic Exoskeletal Orthosis © [IDEO] and Return to

Run Clinical Pathway) had the potential to similarly improve outcomes for members of the military who were injured after 2007.(24-28)

2. Rationale

This study extended the follow-up of the original METALS cohort to examine longer term outcomes and enrolled a new cohort of METALS patients injured in later years of OIF/OEF/OND who may have benefited from improvements in limb salvage care. Analysis of de-identified claims data was proposed to provide a comprehensive comparison of complications and use of services between amputees and limb salvage patients and variations in utilization over time. For the subset of eligible individuals who provided consent to be interviewed, we linked outcome data with data on the long-term use of services provided by the military and VA.

Specific Aims:

1. **To examine the long-term (av. 10-year) functional outcomes following major limb trauma sustained in OIF/OEF/OND and compare outcomes following amputation vs. limb salvage.** We recontacted individuals previously interviewed as part of the original METALS Study (Cohort #1). Hypotheses include:
    a. For lower & upper limb injury, 10-year outcomes would be similar to 3 year outcomes; rates of overall dysfunction, PTSD and depression will be significantly worse than population norms;
    b. For lower limb injury: significant differences found in 3-year outcomes for those undergoing amputation vs. reconstruction would be maintained at 10 years;
    c. For upper limb injury: the comparability of outcomes for limb salvage vs. amputation found at 3-years would be maintained at 10 years.
2. **Compare early (av. 3 years) functional outcomes following major limb trauma for those injured early (2003-2007) with those injured later (2008–2013) in OIF/OEF/OND.** We enrolled a new cohort of METALS-eligible patients (Cohort #2) injured after 2007. We will use qualitative research methods to characterize changes in care and benefits available to amputees and limb salvage patients over the period 2003-2013. With improvement in screening and care over time, we hypothesized that:
    a. Cohort #2 would have improved psychological and functional outcomes compared to Cohort #1.
    b. Outcomes following limb salvage vs. amputation would be more comparable in Cohort #2 compared to Cohort #1.
3. **Examine incidence of short- & long-term complications following major limb trauma.** We accessed archival health services data available through the military and the VA. We hypothesize that:
    a. Rates of complications and persistent morbidity would be higher among individuals undergoing limb salvage vs. amputation; and
    b. Those with persistent morbidity would have poorer functional outcomes at follow-up.
4. **Examine short- and long-term use of medical, mental health and rehabilitation services and compare rates of use between amputees and limb salvage patients in Cohorts #1 and #2.** To address this aim we used the merged data described in Aim #3. We hypothesized that:

a. Use of PT/OT and mental health services would be lower for those undergoing limb salvage vs. amputation.
b. For limb salvage patients, use of PT/OT and mental health services would be higher for those in Cohort #2 compared to Cohort #1.

5. **Determine utilization of care in relation to where study participants live and location of VA and military care facilities to assess access to care and self-perceived unmet need for (and satisfaction with) services.** We proposed to use GIS methods to estimate the distance between the study participant's home and the nearest MTF and VA facilities. We hypothesize that
    a. Individuals living closer to VA and military facilities would have higher rates of service utilization and lower rates of persistent morbidity and self-perceived unmet need.

3. Keywords

Orthopaedic Trauma; Retrospective Cohort study; Extremity Trauma; Amputation; Limb Salvage; Functional Outcomes; Use of Services; Outcomes

4. Methods and Materials

4.1: Overview

This study was conducted as an expansion of the METALS I study, a retrospective cohort study which was completed in 2012 and assessed outcomes for 429 of 829 service members identified who were injured between 2003 and 2007 (referred to as Cohort 1). In the METALS II study, we proposed to (1) examine longer term outcomes (9-13 years post injury) among the METALS I (Cohort 1) participants; (2) examine outcomes for a new cohort of patients, injured between 2008 and 2014 (referred to as Cohort 2); and (3) analyze the use of services of all individuals who meet eligibility criteria between 2003 and 2014.

De-identified archival claims data maintained by the VA and DoD were used to compare service utilization overall for all individuals who were injured between 2003 and 2014 (cohorts 1 and 2) and who met eligibility criteria. Additionally, study participants were contacted asked to consent to a single telephone interview and to allow the study team to access medical records and link this information to the claims data.

The study was approved by the institutional review boards of each military treatment facility, the Johns Hopkins Bloomberg School of Public Health (the coordinating center for the study), the United States Army Medical Research and Materiel Command, Walter Reed National Military Medical Center, the University of Texas Health Science Center San Antonio, the University of Utah, and the DoD Human Research Protection Office.

4.2 Study Population

All individuals who met the study eligibility criteria were included in the analysis of utilization data (Specific Aims 3 & 4). Eligible to be contacted for the interview (Specific Aims 1 & 2) were (1) individuals in Cohort 1 who participated in the original METALS I study and (2) all

individuals in Cohort 2. We obtained a modification of written consent for this study, allowing us to obtain oral consent for conducting interviews and linking interview, medical record, and claims data on participants in the METALS I and METALS II cohort.

Several data sources were used to identify potential participants (for Cohort 2) and obtain or verify contact information (for both Cohort 1 and Cohort 2). These data sources are described below:

- **Department of Defense Trauma Registry (DoDTR)**: Maintained by Joint Trauma System, the DoDTR is the data repository for DoD trauma-related injuries. The registry documents, in electronic format, information about the demographics, mechanism and severity of injuries, treatment, and outcome of injuries sustained by military and civilian personnel in wartime and peacetime from the point of wounding to final disposition.
- **Military Orthopaedic Trauma Registry (MOTR):** MOTR was modeled after the database used for METALS I and contains data on the: (i) classification of all orthopaedic injuries; (ii) treatment, including procedures performed; and (iii) complications. Fractures are classified by the bone segment and fracture type using the AO/OTA classification of long bone fractures. Also documented are: segmental loss, skin defect, burns, muscle/tendon injury, and location/severity of nerve and vascular injuries. Amputations are classified according to level and type of amputation procedure. Some (but not all) of the participants in the METALS II study will already have had data entered into MOTR.
- **Armed Forces Health Longitudinal Technology Application (AHLTA):** The electronic outpatient medical record used by the Department of Defense, contains data on patient encounters and test results, such as labs and radiology reports, but does not contain treatment specific information, such as images and dictated operative reports containing detailed treatment and injury information.
- **Essentris:** The inpatient electronic medical record used at the Military Treatment Facilities, contains all imaging and operative notes for services delivered at that facility.
- **Defense Enrollment Eligibility Reporting System (DEERS)**: A database of personnel and benefits information on active, retired, and reserve uniformed service members.
- **LexisNexis Accurint (www.accurint.com)**: A proprietary database of billions of online public records, which provide precise rank-ordered contact information. The search will match information that is entered (ie. name/social security) and will compile an address, email and phone number history for each person. The service also checks against the Master Death file.
- **Inpatient, outpatient, and pharmacy data from the Military Health System Data Repositiory (MDR)**. These data were used to identify complications and comorbid conditions before and after injury.
- **Inpatient and outpatient data from the VA National data from the VA Corporate Data Warehouse, and pharmacy data from the VA Pharmacy Benefit Management Databas**. These data were used to identify complications and comorbid conditions after injury.

Utilization Analysis Eligibility – Cohort 1: As part of METALS I, which is still an active protocol, the PI retained files containing contact information for all individuals who were attempted contacts in the in the original study (Cohort 1). The METRC MCC used these files to

develop a look up file for the 898 individuals identified as eligible for METALS 1. This file contained information needed to access DoD and VA utilization data (name, date of birth, year of injury, SSN) and an indicator regarding amputation status at the time they were screened for eligibility. Colleagues at the VA, led by Dr. Pugh, used this file to access relevant utilization data to complete address Specific Aims 3 and 4.

Interview Eligibility – Cohort 1: Only those individuals who were located and consented to the METALS I study (n= 429) were contacted for participation in PART B of the current study. For these individuals, contact information previously obtained for METALS I was verified by staff at the USAISR using the DEERS database. The additional contact data will be appended to the original file, and the resulting file transferred to the METRC coordinating center, where staff verified contact information by appending any publicly available contact information using the Accurint service. Deaths were noted and removed from the contact file.

Utilization Analysis and Interview Eligibility – Cohort 2: A HIPAA waiver was obtained for the purposes of screening and contacting potentially eligible participants injured after 2007. Staff at the USAISR ran a data pull of the DOD Trauma Registry, looking for live discharges from San Antonio Military Medical Center or Walter Reed Military Medical Center between 2008 and 2013 with any of the following procedure or ICD codes, excluding cases with an AIS of 5 consistent with a traumatic brain injury:

a. Amputation procedure codes: 84.0 (Excluding 84.01) and 84.1 (excluding 84.11) or one of the following ICD-9CM Dx codes:
b. Open Femur Dx: 821.1, 821.3, 820.1, 820.3, 820.9
c. Open Tibia Dx: 823.1, 823.3, 823.9
d. Open Humerus Dx: 812.1, 812.3, 812.5
e. Open Radius Dx: 813.1, 813.3, 813.5, 813.9
f. Multiple fxs of lower and upper limbs Dx: 828.1
g. Multiple fxs of hand Dx: 817.1
h. Traumatic Amps Dx: 887, 896, 897

Cases resulting from this query were matched by abstractors at the USAISR against records in the MOTR, and screening data was entered into the METRC electronic data capture system, REDCap. If the case did NOT have a match in the MOTR, the USAISR abstractor reviewed the patient's record in AHLTA and Essentris to complete the screening form. Information on inclusion and exclusion criteria for each screened case was entered into REDCap and the case was be assigned a unique METALS II identifier, regardless of eligibility, allowing documentation of screen fails. Staff at the USAISR matched identifiers for cases meeting eligibility criteria against the DEERS database to obtain the most recent contact information available in this system. All available contact data was used to create a contact file, which was transferred to the METALS coordinating center, where staff verified contact information, appending any publicly available contact information using the Accurint service. The METRC MCC used these files to develop a look up file for the 580 individuals identified as eligible in Cohort 2. This file contained information needed to access DoD and VA utilization data (name, date of birth, year of injury, SSN) and an indicator regarding amputation status at the time they were screened for eligibility. Colleagues at the VA, led by Dr. Pugh, used this file to access relevant utilization data to complete address Specific Aims 3 and 4.

4.3 Participant Inclusion Criteria

1. Active-duty service members, reservists and National Guard deployed in the GWOT who sustained major limb trauma (combat or non-combat related) and treated at either San Antonio Military Medical Center or Walter Reed National Military Medical Center;
2. Major limb trauma includes any injury to the upper or lower limb (excluding pelvis or acetabulum) that resulted in a major amputation (at or proximal to the tibiotalar joint in the lower limbs or the radiocarpal joint in upper limbs) or required operative treatment and either:
    a. revascularization,
    b. bone grafting or bone transport;
    c. local or free flap coverage;
    d. repair of major nerve injury (complete deficit of a major nerve to include sciatic, radial, ulnar, medial, tibial, femoral, common peritoneal, superior or deep peritoneal);
    e. complete compartment injury; and/or
    f. compartment syndrome resulting in a fasciotomy .

    These injuries typically include (but are not limited to): traumatic amputations, Gustilo Grade IIIB and IIIC fractures, selected Grade IIIA fractures, dysvascular limbs, major soft tissue injuries, and severe foot and hand injuries.
3. Subjects with major limb trauma (as described above) may have multiple injuries, including, but not limited to injuries to major organs, such as the lungs, kidney, liver, or spleen. Although patients with moderate to severe brain injury will be excluded (see below), patients with mild head injuries may be included.
4. Inclusion will be assessed at the injury level; participants with multiple qualifying injuries may be included, although their outcomes (salvage versus amputation) will be assessed at the limb, not individual level.
5. Aged 18-85

4.4 Participant Exclusion Criteria

1. Contract workers (i.e. non-military personnel)
2. Patients with a moderate to severe traumatic brain injury, defined as a Glasgow Coma Scale (GCS) score < 13 21 days after injury or upon discharge from acute care, whichever comes first.
3. Patients with a spinal cord injury resulting in paraplegia or quadriplegia.

4.5 Contacting Participants and Conducting Interviews

Using the final contact files, the METALS study coordinator sent an envelope bearing the study logo including the following cohort-specific materials: (1) a cover letter signed by the Chief of Orthopaedics at the center where the participant was treated, (2) a study brochure with a brief overview of study procedures and (3) a research information sheet describing the study in greater detail. To encourage participation, the mailing also contained a “challenge coin” designed

especially for the study. Upon completion of the interview (by phone or online), the participant could choose between an electronic gift card or a check for $50.

All materials referenced the study website, metals.metrc.org. The website served purposes: (1) it functioned as a digital version of the study information sheet, and (2) it provided a mechanism for participants to either contact the study team or consent to participate, provide HIPAA privacy authorization to access and link medical and billing records, and complete the study survey online.

Included in the mailing was an opt out form and a stamped return envelope addressed to the METALS coordinating center at Johns Hopkins. Using this form, individuals could elect not to be contacted (opt out of PART B of the study) by making a check mark in the appropriate box. This same functionality was available using a forms function on the study website. The REDCap screening form for all individuals who elected NOT to be contacted were closed by the METALS study manager.

Within 14 days of the mail out, all individuals who did not opt out of the study and who did not consent to study participation using the study website (see below) were contacted by interviewers who were employees of the METALS coordinating center. Each potential number for a non-respondent was be called up to 20 times, including at multiple times of day and day of the week (including weekends). Numbers that were identified by Lexis Nexis as cell phone numbers were be sent a brief text message asking for the participant to contact us "This message is for NAME. We are trying to contact you about a study you may be eligible to participate in. Please call the coordinating center at XXX-XXX-XXXX to discuss further. You may reply "No" if you would like us to stop texting you." Lexis Nexis also provided email addresses associated with these participants. If we were not able to contact a participant by telephone, we sent the introductory letter electronically to the email address on record. Once the study team was able to connect with a participant by telephone, they reviewed study procedures and inquired about whether or not potential participants would be interested in joining the study. If the individual agreed, oral consent to complete the interview, provide access to the full medical record, and link this information to DoD and VA claims data was be obtained by telephone using a prepared script. The interviewer documented consent in the REDCap screening form and proceeded to document interview responses electronically in the REDCap interview case report form. Following the interview, study participants were sent documentation of their oral consent to acknowledge their participation in the interview and to serve as confirmation of their enrollment into the study. A copy of this verification was also retained on file at the METALS coordinating center.

Participants who accessed the study website provided consent to participate, completed a HIPAA privacy authorization for accessing medical and billing records, and completed the study survey online. The website had a secure log-in area, which any participant could access using the study-id on the introductory letter. The secure area of the website provided an opportunity to review study procedures and provide consent, at which point the participant could begin the survey. Alternatively the participant could elect NOT to participate and this was recorded, with no further contact made with the participant.

We received a HIPAA Waiver of the requirement to obtain a signed privacy authorization for accessing medical records and billing data for any individual who did not visit the study website. The research could not practicably be conducted if we required written access for accessing this information. Participants were widely dispersed geographically, were not currently being seen at the original centers where they were treated, and would not be seen in person. Obtaining a signed authorization for each individual who responded to the verbal interview would result in a low response rate and loss of data for participants who had already given their assent to participate. No linkages will be made to identifiable information for any participant who does not provide consent to participate.

Of the 612 interviews completed, 160 (26%) were completed by telephone and 452 (74%) were completed online.

Due to a concern of low follow-up rates in our original sample and the potential for a biased result between responders and non-responders, the study team conducted an early analysis of utilizations, comparing these two groups. VHA inpatient, outpatient, and pharmacy data were obtained for all individuals who were identified as eligible for the METALS study and who received VHA care within five years of injury. Available data included military and sociodemographic characteristics, diagnosed health conditions, and prescribed medications documented in VHA care. Health conditions diagnosed during the five-year study interval, including physical and mental health conditions, were identified based on the presence of two or more International Classification of Disease, 9th Revision Clinical Modification (ICD-9-CM) codes in the inpatient or outpatient setting. Central nervous system (CNS) medication polypharmacy was identified by any patient receiving prescriptions for medications from two or more of the following drug classes in a one-year period: atypical antipsychotic (i.e. clozapine), antidepressant (any type), benzodiazepine, sedative hypnotic (i.e., zolpidem), or opioid pain medication. Differences in demographic characteristics, rates of diagnosed health conditions, and rates psychotropic polypharmacy between responders and non-responders (i.e., refused and non-responders) were compared using 99% confidence intervals (α=0.01 due to the number of comparisons).

Of the 786 individuals identified as eligible and who could be located in the original METALS study, 679 (86.4%) had entered the VHA system within five years of injury and had data available to contribute to this analysis. Of these individuals, 378 (55.7%) were responders and 301 were non-responders (44.3%), which is a similar to the composition of responders (56.2%) and non-responders (43.8) in the 786 individuals originally approached for participation in the METALS study. The proportion of individuals entering the VHA system (n=679) was similar between responders and non-responders (85.5% and 87.5%, respectively). There was little difference in mean time from entry to VHA care between responder (9.9 months; 99% CI: 8.7 – 11.8) and non-responder (10.6 months; 99% CI: 8.9 –12.7) groups.

Among the 391 amputees in the VHA sample, 209 (53.5%) completed an interview (responders). For the 288 limb salvage patients in the VHA sample, 169 (58.7%) completed an interview (responders). These proportions are slightly different than those observed in the original METALS study, where the response rate was 64% among amputees and 55% among salvage patients.

Overall, the group of METALS-eligible participants who entered the VHA system within five years of injury was 96.9% male and 73.8% white. Of the potential participants, 12.1% had attended at least one year of college. The group was comprised of service members from the Air Force (<1%), Army (72.8%), Marines (23.9%), and Navy or Coast Guard (2.5%). Although responders were older than non-responders, with an average age at injury of 26.0 (99% CI: 25.2 – 26.9) and 24.7 (99% CI: 23.8 – 25.5), respectively, these differences are likely not clinically important. There were no other significant differences between groups in terms of demographic variables.

No significant differences were observed between the groups with regard to diagnosis of a physical or mental health condition or prescription of psychotropic medications in the five years after injury following entry to the VHA. Overall, 14.1% were diagnosed with an acute infection and 3.7% with a chronic infection, and 24.5% service members were diagnosed with one or more physical health effects (e.g., diabetes, hypertension, lung disease) in the VA within five years of injury. There were comparatively high rates of diagnosis for traumatic brain injury (36.5%), depression (22.4%), post-traumatic stress disorder (54.8%) and substance use disorder (9.9%), with no significant difference between responders and non-responders. There was no variation in prescription of opioids (51.0%) or psychotropic medications (49.2%) during the five years following injury.

We concluded that despite low response rates in the METALS study, there were few differences between groups classified by original study response status. These results were presented at the 2018 MHSRS meeting in Kissimmee, FL.

4.6 Data Collection

The data collected from the interviews are briefly described below:

Characteristics of the Patient and Exposure to Combat Experiences. Because treatment assignments are not randomized in this study, it was important to characterize the patients undergoing amputation and limb salvage and to adjust for any differences in the analysis. Information collected included:

- Demographics including: age; gender; race/ethnicity; military service and grade; education; marital status
- Current annual personal income (from all sources) and health insurance status.
- Perceived adequacy of emotional support measured using a single item assessing perceived support used in the Behavioral Risk Factor Surveillance System (BFRSS).(29)
- Resilience will be measured using a two-item short form of the Connor-Davidson Resilience Scale (CD-RISC).(30)
- Health Habits including smoking history and drinking habits. Standard questions are used to categorize respondents as non-smokers and smokers and frequency and amount of alcohol consumed; the 4-item CAGE instrument(31) is used to screen for possible alcohol abuse.
- Self-reported health problems

- Exposure to combat experiences is assessed using a two-item instrument that is part of the Post Deployment Health Assessment.(32)

Function: Several self-report measures were used to assess functional outcomes, participation in a major role activity, participation in sport and leisure activities and symptoms of depression, post-traumatic stress and chronic pain among all participants who consented to participate in the study. These measures are briefly described below:

- The Dysfunction Index of Short Musculoskeletal Functional Assessment (SMFA) was used to assess Physical Function.(33) The SMFA was developed specifically to measure function in individuals with a wide range of musculoskeletal impairments and provides an overall dysfunction score together with four subscores that summarize: mobility, arm and hand function, daily activities, and emotional status. The SMFA has been well tested for reliability, validity and responsiveness to changes over time.
- Participation in a major role activity was assessed using standard questions that ask about a person's major usual activity in the past week (e.g. active military duty, work, school, taking care of a home); the Work Productivity and Activity Impairment (WPAI) (34-35) was administered to assess productivity at work and in everyday activities. The validity of the WPAI has been established in a number of diseases.
- The Patient Health Questionnaire (PHQ-9) (36) was used to assess the presence of depressive symptoms. The PHQ-9 a well-validated tool for assisting clinicians in diagnosing depression, will be used to measure depressive symptoms. There are two components of the PHQ-9: (1) assessing symptoms and functional impairment to make a tentative depression diagnosis, and (2) deriving a severity score. The PHQ-9 is based directly on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV) A score of >9 is considered positive for depressive symptoms.
- The Military Version of the PTSD Checklist (PCL) (37-38) was used to assess symptoms of post-traumatic stress. The PCL is a 17-item measure that elicits responses for each of the DSM-IV disorders that comprise the diagnostic criteria for PTSD. In accordance with published guidelines, respondents will be identified with probable PTSD if they: (1) experienced at >= 1 re-experiencing /intrusive symptom, >= 3 avoidance experiences and at >= 1 symptom of hyper- arousal, all at the moderate/extreme level (>=3); and (2) reported substantial distress (i.e. total PCL scores >= 50).
- The Chronic Pain Grade (CPG) scale, developed by Von Korff et al (39) was used to grade the severity of chronic pain. It combines 3 items on intensity of pain, a question on the number of disability days and 3 items on interference with daily activities to classify individuals into one of 5 pain grade categories.

Utilization and Complications: Data from interviews and from medical utilization sources were used to assess the incidence of complications and utilization and adequacy of key resources such as rehabilitation services.

- Complications. Incidence of complications were assessed using claims data based on ICD-9/10 codes in DoD and VA health system data.

- Use and Unmet Need for Health & Rehabilitation Services. Use of services within the military health system or the Veteran's Administration Health System was extracted from claims data, and unmet need for services assessed from interview data.
- Standard questions were included in the patient interviews to ascertain self- reported use of inpatient and outpatient health and rehabilitation services during the past year, allowing us to identify services received outside the military or VA systems so that we can judge the extent to which data analyzed from the DoD and VA archival databases will be biased. Participants were also asked if they felt they needed more services (of specific types), and if so, what interfered with their ability to obtain more.
- Use and satisfaction with orthotic and prosthetic devices. Current use of a prosthesis and/or orthosis was ascertained by asking number of hours the device is used per day and number of days device is worn during a typical week (of particular interest will be the identification of individuals who have been fitted with an IDEO). Satisfaction with the devices was assessed using the Orthotics and Prosthetics Users' Survey (OPUS) (40).

4.7 Abstraction of Clinical Data

Following completion of the interview, all interview data, identified by METALS study identifier, was sent by Johns Hopkins to the JTS, where MOTR abstractors completed data abstraction for participants in Cohort 2 who had not previously been entered. Detailed data about the injury and its initial acute treatment were abstracted from Essentris using the standardized data collection protocols developed for MOTR. MOTR was modeled after the database used for METALS I and contains data on the: (i) classification of all orthopaedic injuries; (ii) treatment, including procedures performed; and (iii) complications. Fractures are classified by the bone segment and fracture type using the AO/OTA classification of long bone fractures. Also documented are: segmental loss, skin defect, burns, muscle/tendon injury, and location/severity of nerve and vascular injuries. Amputations are classified according to level and type of amputation procedure. 100% of all interviewed participants were subsequently entered in the MOTR.

However, due to movement of the MOTR from the USAISR to the JTS and the lack of an investigator at the USAISR following multiple staff changes, the study team was not able to establish a data sharing agreement and obtain these data during this period of performance. The investigators will keep the protocol open in the event that future funding comes available to access these data.

4.8 Developing a Merged Data File

Under the direction of Dr. Pugh at the VA, the team used the look up files to compile claims data from the DoD and Veterans Health Administration using the **Department of Defense and Department of Veterans Affairs Infrastructure for Clinical Intelligence (DaVINCI)** behind the VA firewall, developed the analytic dataset and conducted the analysis for Specific Aims 3 and 4. The analysts at the VA also served as the honest broker of all data, under a data sharing agreement established between Johns Hopkins and the VA, merging all interview data with

utilization data, removing all identifiers, and retaining a crosswalk file that would allow future identification of participants in the study. The final, deidentified analytic dataset will be retained at the METRC coordinating center and at the VA.

5. Accomplishments

5.1: Major Tasks

Task 1: Regulatory Review	**Status**
Subtask 1: Finalize protocol	Complete
Subtask 2: Develop and execute necessary MOUs and CRADAs	Complete
Subtask 3: Obtain IRB approval from JHU BSPH; SAMMC/CFI; HSR/STVHVCS and WRNMMC - to be done in phases	Complete
Subtask 4: USAMRMC Human Research Protections Office review and approval	Complete
Task 2: Revise Interview and Develop Recruitment Procedures	
Subtask 1: Conduct Focus Groups	Complete
Subtask 2: Revise Interview	Complete
Subtask 3: Develop recruitment materials	Complete
Task 3: Training Research Staff	
Subtask 1: Train interviewers	Complete
Subtask 2: Train MOTR medical record abstractors	Complete
Task 3: Obtain Contact Information for Cohort # 1	
Subtask 1: Assemble information from METALS 1	Complete
Subtask 2: Access contact data from VBA, DEERS, AHLTA, DoDTR	Complete
Task 4: Identify Cohort #2 and Abstract Clinical Information into MOTR	
Subtask 1: Search DoDTR for potentially eligible participants	Complete
Subtask 2: Access MOTR or ESSENTRIS to confirm eligibility	Complete
Subtask 3: Access contact data from VBA, DEERS, AHLTA, DoDTR	Complete
Subtask 4: Abstract SAMMC/WRNMMC medical records through ESSENTRIS	Complete
Task 5: Contact, Consent and Interview Participants	
Subtask 1: Contact, consent and Interview Cohort #1	Complete
Subtask 2: Contact, consent and Interview Cohort #2	Complete
Task 6: Access and Link Data from DoD and VA	
Subtask 1: Access records from the DoD Military Data Repository (MDR)	Complete
Subtask 2: Link data from MDR and VA and develop analysis file	Complete
Subtask 3: Access geospatial data and link data from the Census bureau and Agency for Healthcare Research and Quality (AHRQ) data on county level resources	Was not feasible
Task 7: Conduct Qualitative Study on Approaches to Treatment over Time	
Subtask 1: Identify key informants and documents	50% complete

Subtask 2: Abstract documents interview informants	50% complete
Task 8: Data Analysis and Report Writing	
Subtask 1: Develop analysis files: Interview Data	Complete
Subtask 2: Develop analysis files: Acute Treatment (MOTR)	Was not feasible
Subtask 3: Develop analysis files: DOD/VA Health Services and Morbidity Data	Complete
Subtask 4: Develop analysis files: Data for Spatial Analysis	Was not feasible
Subtask 5: Conduct analyses relevant to specific aims of the study	Complete

5.2 Accomplishments

Major Activities:
Task 1-5: Obtain regulatory approval, identify contact and interview study participants
All activities associated with Tasks 1-5 were completed.

A total of 1,007 potentially eligible participants were identified (424 from M1, 580 from M2). Among these participants, no contact data were available for 188 (M1: 64, M2: 124), for a total denominator of 819 attempts. Although the unadjusted response rate was 61% (M1: 67%, M2 56%), among the 819 participants with available contact information, 612 interviews were completed (74.7%) (M1: 286/360 (79.4%); M2: 326/456 (71.5%)).

The study abstractor employed through the Geneva Foundation completed data entry of eligible, consented participants into the Military Orthopaedic Trauma Registry (MOTR) and data entry is complete. However, due to changes in data ownership and personnel, we were unable to identify a principal investigator to support the data use agreement that would allow us to obtain these MOTR data as part of this project. Specifically, the data moved from the USAISR to the Joint Trauma System, making access more difficult. The VA investigator in San Antonio moved to the VA in Utah and no longer had the same data access. In pursuing the appropriate data sharing agreement, multiple changes of investigators at the USAIR resulting in a lack of a sponsor for the project proved to be insurmountable, and the study team was not able to establish a data sharing agreement nor obtain detailed clinical information from the MOTR data.

This was a disappointing outcome, however, due to the fact that we collected detailed data on injury severity (including all Abbreviated Injury Scale codes) and amputation vs limb salvage status as part of the initial screening, we are able to categorize all eligible participants as either a limb salvage or amputation of the upper or lower extremity. The main impact of this loss of data has been an inability to reliably determine which participants have bilateral injuries or both upper and lower injuries.

Task 6: Access and Link Data from DOD and VA

We used identifiers from the Johns Hopkins team for individuals who met criteria for inclusion and those who had interview data available. Using those data, we obtained inpatient, outpatient and pharmacy data from the Military Data Repository and VA Corporate Data Warehouse

through the DaVINCI platform. We identified diagnosed medical and mental health conditions before and after the year of injury for those with documented date/year of injury. Date of injury was available for the original METALS cohort and year of injury was available for METALS 2. Individuals without information on year/date of injury (n=6) were excluded from the heath system data analysis as it was not possible to clearly identify outcomes of injury. Using these criteria, there were 1,502 individuals in the overall cohort using health system data (n=972 METALS 1; 530 METALS 2; One individual was in both cohorts, so we included him in the cohort of first injury).

Task 7: Conduct a Qualitative Study on Approaches to Treatment over Time

Our initial strategy was to qualitatively examine care practices documented in MOTR. While not crucial to our Specific Aims, this analysis could have theoretically provided interesting information on possible contributions to differences in outcomes between Cohort #1 and Cohort #2, if identified. The completion of this task was hindered by the final access to MOTR output. However, Dr. Rivera, having worked extensively with MOTR data, noted that inflections in care that may be attributable to deployed clinical practice guidelines would be difficult to capture without access to Role 2 data. Given that MOTR contains some Role2b but largely Role 3-5 data, we concluded that we may not be able to confidently address this task even with full access to MOTR output.

Task 8: Data Analysis and Report Writing

This process is ongoing. The submission of this report concludes the analysis of data related to Specific Aims 1-4. Unfortunately, Specific Aim 5 will not be completed due to changes in personnel and availability of data since the number of individuals in each county was to sparse to accurately calculate estimates for spatial analyses. This information was shared early in the project with the study program officers. Results from each aim will be written up as a manuscript and results submitted to the Orthopaedic Trauma Association and the MHSRS to facilitate dissemination.

5.3 Key Results

Description of study population: A total of 995 participants were originally identified as eligible in the initial METALS study and 583 individuals were identified as eligible as part of cohort 2, with a single person who was included in both cohorts. Of these 1,578, 76 were found to be ineligible, were deceased, or had no records in the VA or DOD data, bringing the total sample of eligible participants to 1,502 (966 cohort 1, 536 cohort 2). This is the population that was used to conduct analysis related to specific aims 3 and 4, as well as part of the analysis for specific aim 2.

Of these cases, 1,007 individuals were searched for contact information (424 who had previously participated as part of cohort 1, 583 newly identified for cohort 2). Of these individuals, 3 were found to be deceased, 1004 were contacted by letter. Overall, 612 responses were obtained, a 61% response rate was achieved, although this rate was higher for cohort 1 (67%) than cohort 2 (56%), which is explained by the fact that cohort 1 had previously participated. This is the

population that was used to conduct analysis related to specific aim 1, and will be used for the functional outcome analysis for specific aim 2.

Table 1: Response Rates

	Total	Deceased	Complete interview	Online (% of completed interviews)	By Phone (% of completed interviews)	Refusals	Not located
Total	1007	3 (<1%)	612 (61%)	452 (75%)	155 (25%)	202 (20%)	190 (9%)
M1	424		286 (67%)	196 (68%)	90 (32%)	74 (18%)	64 (15%)
M2	583	3 (<1%)	326* (56%)	256 (78%)	65 (22%)	128 (22%)	126 (22%)
*includes 5 partial completes							

Table 2 describes the demographic information of the two cohorts at baseline (note that for cohort 1, these data were collected as part of the M1 study). The majority of the study participants were active duty Army (74%) or Marines (17%); 4% were National Guard or reservists. The M1 cohort had more Marines and National Guard/reservists, and the M2 had more members of the Army. The groups were similar in terms of rank, although there were slightly more (25% vs 20% senior officers in the M2 cohort than the M1 cohort, and the M2 cohort was more likely to report high combat intensity, although the measures were slightly different between the cohorts. Seven percent of participants report having personal incomes of less than $20,000; 68% report incomes greater than $50,000. (Table 2)

Table 2: Demographics

	Total (N=612)	M1 (N=288)	M2 (N=324)
Age at Time of Injury, Mean (SD)	26.1 (6.0)	26.7 (6.7)	25.5 (5.1)
Race/ethnicity			
Hispanic	96 (16%)	51 (16%)	45 (16%)
Non-Hispanic, African American	37 (6%)	24 (7%)	13 (5%)
Non-Hispanic, White	441 (73%)	230 (72%)	211 (74%)
Non-Hispanic, Other	33 (5%)	16 (5%)	17 (6%)
Unknown	5	3	2
Education			
<HS	12 (2%)	11 (3%)	1 (<1%)
HS or GED	165 (27%)	106 (33%)	59 (20%)
Some college	435 (71%)	207 (64%)	228 (79%)
Military Branch			

Army	443 (74%)	212 (66%)	231 (85%)
Navy	18 (3%)	14 (4%)	4 (1%)
Marines	101 (17%)	74 (23%)	27 (10%)
Air Force	10 (2%)	2 (1%)	8 (3%)
National Guard/Reserves	23 (4%)	21 (7%)	2 (1%)
Unknown	17	1	16
Highest Pay Grade			
E1-E4 (Junior Enlisted)	199 (33%)	108 (33%)	91 (32%)
E5-E6 (Midlevel Enlisted)	271 (45%)	150 (46%)	121 (43%)
E7-E9/W1-W5/O1-O10 (Senior Enlisted/Officers)	137 (23%)	65 (20%)	72 (25%)
Unknown	5	1	4
Income			
Less than $20K	42 (7%)	28 (9%)	14 (5%)
Less than $40K	146 (25%)	105 (35%)	41 (15%)
Less than $60K	175 (30%)	80 (27%)	95 (34%)
Less than $80K	119 (20%)	43 (14%)	76 (27%)
Less than $100K	47 (8%)	15 (5%)	32 (11%)
More than $100K	54 (9%)	30 (10%)	24 (9%)
Unknown	29	23	6
Combat Exposure†			
0	5 (1%)	4 (1%)	1 (<1%)
1	44 (7%)	33 (10%)	11 (4%)
2	157 (26%)	96 (30%)	61 (21%)
3	406 (66%)	191 (59%)	215 (75%)
	Total (N=612)	M1 (N=286)	M2 (N=326)

†Measured differently in M1 and M2.

Health habits and risk factors (reported at the time of follow-up) are summarized in Table 3. The percent of patients who screened positive for a possible alcohol problem (based on endorsement of 1 or more of the CAGE items) was 29%, with higher numbers (38% vs 22%) for the M2 cohort. The percent of participants in the Millennium Cohort Study (of those who had deployed with combat exposure) who screened positive for a possible alcohol problem was 19.4% which is lower than that observed in the METALS study (41). The percent of METALS participants who were current smokers is higher (42%) than the general population of males ages 18-44 (27.3%) (42). The percentage of current smokers is higher than the 19.4% reported in the Millennium Cohort Study (of those who had deployed with combat exposure). These numbers are similar across both cohorts.

Table 3: Health Habits and Risk Factors

	Total (N=612)	M1 (N=286)	M2 (N=326)
Comorbidities (0, 1-2, 3+)			
0	427 (75%)	276 (88%)	151 (58%)
1-2	114 (20%)	28 (9%)	86 (33%)
3+	32 (6%)	8 (3%)	24 (9%)
Unknown	39	12	27
CAGE			
0 (no drinking problem)	2 (71%)	252 (79%)	180 (63%)
1 (possible drinking problem)	66 (11%)	29 (9%)	37 (13%)
2 or more (probable drinking problem)	112 (18%)	41 (13%)	71 (25%)
Unknown	2	2	0
Current Tobacco Use	258 (42%)	133 (41%)	125 (43%)
Resilience (CD-RISC-2)*			
0-5	-	-	77 (27%)
6	-	-	67 (23%)
7	-	-	33 (11%)
8	-	-	111 (39%)
Social Support†			
Low	118 (19%)	87 (27%)	31 (11%)
Mid	255 (42%)	116 (36%)	139 (48%)
High	239 (39%)	121 (37%)	118 (41%)

* Not measured in M1

Of the patients in the analytic set, 55% sustained one or more METALS eligible injuries to the lower extremities only (i.e. no METALS eligible upper extremity injury, where in cohort 2 this was defined as having an injury of AIS 3 or greater); 18% sustained one or more METALS eligible injuries to the upper extremities only (i.e. no METALS eligible lower extremity injury); and 27% sustained METALS eligible injuries to both the lower and upper extremities. Possibly due to the differences in definitions of injury, we found differences in the distribution of these injuries by cohort: M1 had 64% with an isolated lower extremity injury, 24% with an isolated upper extremity injury, and 12% with a combination, whereas M2 had 44% with an isolated lower extremity injury, 10% with an isolated upper extremity injury, and 46% with a combination.

Specific Aim 1: Examine the long-term (av. 10-year) functional outcomes following major limb trauma sustained in OIF/OEF/OND and compare outcomes following amputation vs. limb salvage.

We recontacted individuals previously interviewed as part of the original METALS Study (Cohort #1) and included individuals we were able to contact at both timepoints. The original METALS study found that self-reported functional outcomes (Short Musculoskeletal Function Assessment (SMFA) [13] at 38.9 ±13.7 months post-injury) following major lower extremity trauma sustained during military combat operations and compared outcomes for patients treated with amputation versus limb reconstruction. SMFA scores were poor overall compared to population normative scores, but adjusted analyses indicated that service members treated with unilateral lower extremity amputation had better SMFA outcomes than those treated with limb reconstruction. These findings were counter to other publications, such as the Lower Extremity Assessment Project (LEAP), [14] where no significant functional outcome differences were identified between these patient populations. The purpose of the analysis for Specific Aim 1 was to follow the METALS 1 cohort several years later to determine whether longer term functional outcomes changed over time and whether differences in outcome by treatment persist. We hypothesized that outcomes would have improved overall and that significant differences found in early outcomes for those undergoing amputation versus reconstruction would be maintained long-term.

For this paper, we focused on 307 individuals who had sustained METALS eligible injuries to the lower limbs and for whom complete information at the initial contact (T1) was obtained, of whom 212 (69.0 %) responded to the follow-up contact (T2) either by phone (n=71) or online (n=141). Those who agreed to the T2 assessment were similar in most respects to those who did not, except those who responded at T2 were slightly older (80.7% of those completing both T1 and T2 assessments were 25 years or older compared to 68.4% of those who were lost to follow-up at T2) ($p < 0.05$). (Table 1)

The mean time between the first (T1) and second contacts (T2) was 117.8 months (range: 94.2-141.7 months). The average time of the second contact from injury was 155.9 months (range: 119.2-187.6 months).

Of the 212 patients who were followed at T2, 119 (56%) had one or both limbs amputated and 93 (44%) had both limbs reconstructed. Between T1 and T2, six patients underwent a late amputation for pain, poor function and/or infection.

Specific Aim 1, Table 1: Characteristics of study cohort

	Letters Sent	**Interviewed Time 1 and Time 2**	**Non-reponders**	**Comparison of Responders & Non-responders***
	N=307 (%)	**N=212 (%)**	**N=95 (%)**	**p-value**
Mean Time of 1st Interview (T1) from Injury (months)	37.5 (13.5)	38.0 (13.6)	36.5 (13.1)	0.36
Mean Time of 2nd Interview (T2) from Injury (months)	NA	155.9 (15.0)	NA	NA

Lower Extremity Amputation at T1				
Yes	55.4%	56.1%	53.7%	0.71
Age at T1				
18-24	23.1%	19.3%	31.6%	0.05
25-29	36.2%	36.8%	34.7%	
>=30	40.7%	43.9%	33.7%	
Mean Age (SD)	29.9 (6.9)	30.3 (6.5)	28.9 (7.6)	0.10
% Male	97.1%	96.7%	97.9%	0.73
Race/Ethnicity				
Non-Hispanic White	72.4%	71.9%	73.4%	0.09
Non-Hispanic Black	7.9%	10.0%	3.2%	
Hispanic	14.5%	14.3%	14.9%	
Other	5.3%	3.8%	8.5%	
% High School Graduate or Less at T1	35.2%	34.0%	37.9%	0.52
Marital Status at T1				
Married	57.7%	58.0%	56.8%	0.29
Never Married	28.0%	25.9%	32.6%	
Separated/Divorced/Widowed	14.3%	16.0%	10.5%	
Social Support at Time 1				
Low (0-70)	27.0%	29.7%	21.1%	0.27
Moderate (71-80)	35.8%	34.0%	40.0%	
High (81 – 100)	37.1%	36.3%	39.0%	
Mean Score (SD)	73.9 (11.8)	73.6 (11.8)	74.5 (11.8)	0.51
Military Grade (highest while on active duty)				
Junior Enlisted (E1 – E4)	32.7%	29.3%	40.4%	0.11
Midlevel Enlisted (E5 – E6)	46.4%	47.6%	43.6%	
Senior Enlisted (E7-E9)/Officers	20.9%	23.1%	16.0%	

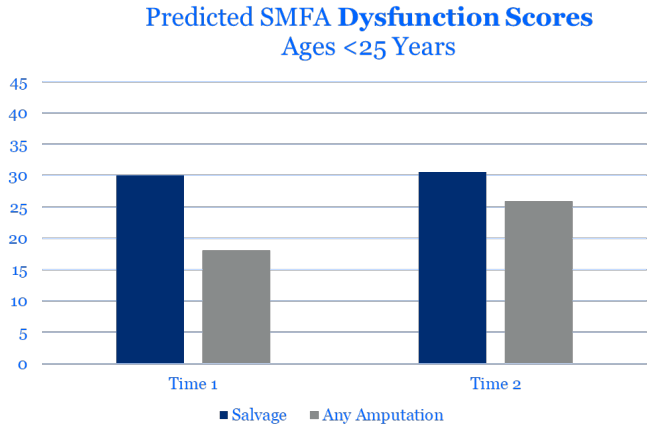
Combat Experiences (during deployment)				
1-5	18.6%	19.3%	16.8%	0.97
6-8	20.5%	20.3%	21.1%	
9-11	25.7%	25.5%	26.3%	
12-17	35.2%	34.9%	35.8%	
Mean Score (SD)	9.5 (3.8)	9.4 (3.9)	9.6 (3.8)	0.69
* T-test, X2 or Fisher's exact				

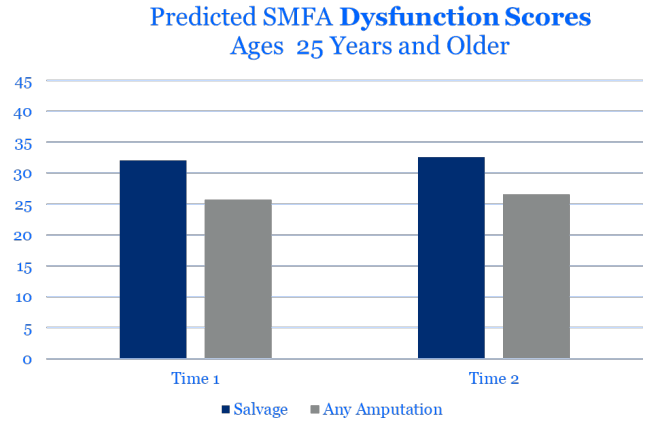
Outcomes observed at T1 and T2 were first compared across five principal treatment groups where treatment was defined at T1: (1) unilateral salvage (n=85), (2) unilateral amputation (n=81), (3) bilateral amputation (n=17), (4) bilateral salvage (n=8), and (5) bilateral injuries with an amputation on one side and salvage on the other (n=21). Due to the small numbers of participants with bilateral injuries, T1 and T2 outcomes were compared for those with and without any lower limb amputation. Given the potential bias introduced by the lower participation at T2 among younger participants, differences in T1 and T2 outcomes were also stratified by age at time of injury (less than 25 and 25 or older).

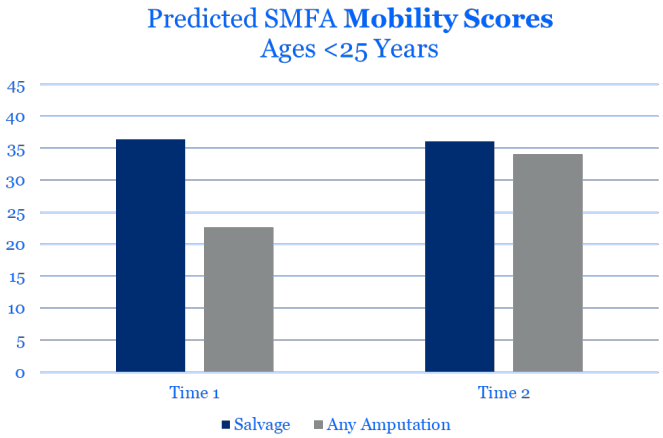
Linear mixed-effect (LME) models were used to measure the overall effect of covariates on outcomes while accounting for the clustering of responses within each patient. LME models account for the correlation of repeated measurements (at T1 and T2) within each subject and estimate the between-subject and within-subject variability in the data, and an interaction of years to interview and amputation at T1 was included to estimate the potential difference in T1 and T2 outcomes by amputation status. Odds ratios and their 95% confidence intervals were estimated by generalized linear mixed models for dependent binary variables. The regressions were performed removing the six participants who had an amputation between T1 and T2 to judge the sensitivity to the results of these late amputations.

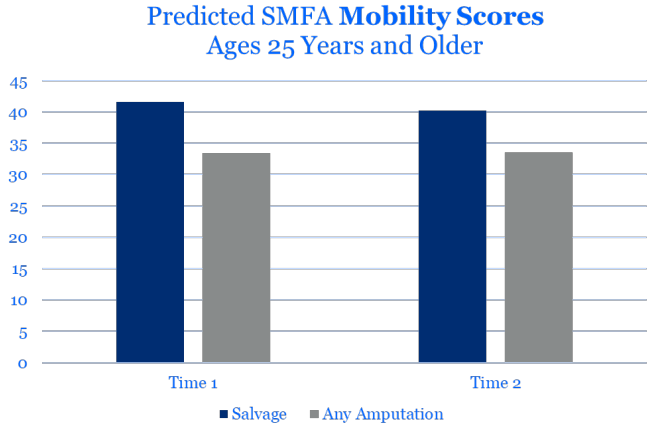
At an average of 13 years post-injury, study participants still reported moderate to high levels of both physical and psychosocial impairment following major lower limb trauma. Over all participants, there was little change in outcomes over time. However, results differed by age and by treatment. Younger participants (age <25) who underwent amputation at T1 had significantly worse SMFA outcomes at T2 compared to T1 while outcomes for salvage patients did not change, rendering outcomes at T2 similar by treatment (contrary to our hypothesis that a treatment differential would persist long-term). For older participants (>= 25 years) SMFA outcomes remained the same at T2 compared to T1. While there were trends towards increased work participation for younger participants and lower percentage screening positive for PTSD, differences were not significant for either age group or treatment group.

Regression Adjusted SMFA Scores by Time and Age Group









Full results and methods will be reported in a manuscript which is under preparation. Further, the significant interaction term between time to interview and amputation status indicates that the increase in SMFA scores over time was significantly larger for amputation versus limb salvage participants. For participants 25 and older, there were no significant differences over time by amputation status. For both age groups, there were no differences by amputation status in percent who screened positive for PTSD or percent who were working. As was true in the original analysis of outcomes at T1, the presence of a strong social support network and fewer combat experiences were associated with better outcomes. To highlight the difference in SMFA scores over time by amputation status, adjusted means (derived from the regression models) are summarized in Figure 1. A unique finding in this study is that the decline between T1 and T2 for the participants with amputations is accounted for by the youngest patients. Among the young patients studied, the onset of secondary health effects at a relatively young age versus the expected onset in a non-trauma population and the cumulative years lived with post-traumatic sequelae of limb loss could account for the decline identified.

At Time 2, 74% of participants with an amputation were wearing their prosthesis 12 or more hours a day; only 10 participants were not using their prosthesis at all. 80% scored 7 or more on a scale of overall satisfaction with their prosthesis from 0 (not at all satisfied) to 10 (completely satisfied); 92% agreed or strongly agreed that their prosthesis made a difference in what they could do. Participants were generally satisfied with the comfort, manageability, ease of donning and doffing, cosmesis, and durability of their prosthesis. They were less satisfied with the cost of purchasing and maintaining their prosthesis, the effect of the device on clothing and the irritation and pain associated with the device.

Specific Aim 2: Compare early (av. 3 years) functional outcomes following major limb trauma for those injured early (2003-2007) with those injured later (2008–2013) in OIF/OEF/OND.

We enrolled a new cohort of METALS-eligible patients (Cohort #2) injured after 2007 and used qualitative research methods to characterize changes in care and benefits available to amputees and limb salvage patients over the entire time period between 2003-2013. With improvement in screening and care over time, we hypothesized that c*ohort #2 would have improved psychological and functional outcomes compared to cohort #1*

An analysis was performed among individuals who experienced major upper and/or lower limb trauma and subsequently consented to participate in the METALS I & II studies. We acquired interview responses from Cohort #1 (2003-2007) & Cohort #2 (2008-2013) surveys, which contained Veteran demographic and social characteristics, military service details, employment information, amputation/salvage status, as well as functional outcomes. Veteran data was then linked between different survey time points. Major limb trauma was defined as injury at or proximal to either the hindfoot or the radiocarpal joint that resulted in an amputation or that required surgical interventions to achieve limb salvage. This included arterial revascularization procedures, bone-grafting and stabilization, muscle flap coverage, nerve repair or grafting, and treatment for extremity compartment syndrome. Patients were excluded from either cohort if they experienced a traumatic brain injury with GCS<15 at discharge, spinal cord injury with persistent paralysis, and those who were not able to respond to the surveys for any other reason**.**

Multiple linear regression analyses used to assess the relationship between changes in functional outcomes over time between M1 and M2 cohorts while adjusting for covariates of time between injury and interview, age, paygrade, level of education, social support, and combat experience. Additionally, Participants in Cohort #1 and #2 were compared in univariate analyses based on demographics, injury status, and assessment of participants mental health, substance abuse, and major complications sustained following major limb injury. Mental health outcomes included anxiety, depression, PTSD, and suicide attempts. Substance abuse outcomes included opioid use disorder, alcoholic use disorder, and hospitalization for overdose. Major complications related to traumatic injury that were assessed included infection and wound-related complications, pulmonary embolism, non-union fracturs, neuropathy or paresthesia, and persistent pain in affected limb or other joints. For continuous variables, an unpaired t-test or the one-way analysis of variance (ANOVA) test was used. Categorical variable analyses were completed with a chi-squared or a Fisher's exact test, depending on factor level combinations of more or less than five, respectively.

Participants in cohort #2 were similar in age and sex to cohort #1, but more likely to be Caucasian race and serve in the Army branch of the military (Specific Aim 2 - Table 1). Further, individuals in cohort #2 were significantly more likely to suffer from depression, anxiety, post-traumatic stress disorder, and substance use disorders (all P<0.05) before incurring their injury. There was a significantly lower rate of upper and lower limb amputations among participants in cohort #2 vs. cohort #1 along with a corresponding increase in limb salvage. Nevertheless, there was a higher proportion of patients in cohort #2 that required multiple limb amputations.

Specific Aim 2 -Table 1: Comparison of demographics and injury status between METALS I and II cohorts

Variables	METALS I – Cohort (n=324)	METALS II – Cohort (n=288)	P-value
Demographics			
AGE (Injury Year), mean (SD)	26.7 (6.7)	25.5 (5.1)	0.019
MALE SEX	97.20%	97.40%	1
RACE/ETHNICTY			0.478
Non-Hispanic White	71.7%	73.8%	
Non-Hispanic Black	7.5%	4.6%	
Hispanic	15.9%	15.7%	
Other	5.0%	5.9%	
MILITARY GRADE (highest while on active duty)			0.299
Junior Enlisted (E1 – E4)	33.4%	32.1%	
Midlevel Enlisted (E5 – E6)	46.4%	42.6%	
Senior Enlisted (E7-E9)/Officers	20.1%	25.4%	
% High School Graduate or Less	36.10%	20.80%	<0.001
MARITAL STATUS			<0.001
Married / Living with Partner	57.7%	73.3%	
Separated / Divorced	13.0%	14.2%	
Never Married / Widowed	29.3%	12.5%	
SOCIAL SUPPORT			
Low (MSPSS 0-70)	26.9%	10.8%	
Moderate (MSPSS 71-80)	35.8%	48.3%	
High (MSPSS 81 – 100)	37.4%	41.0%	
COMBAT EXPERIENCES			<0.001

0	1.2%	0.4%	
1	10.2%	3.8%	
2	29.6%	21.2%	
3	59.0%	74.7%	
MEAN TIME FROM INJURY to INTERVIEW (months) mean (SD)	37.5 (13.8)	91.8 (18.3)	<0.001
LOWER EXTREMITY AMPUTATION	56.2%	64.90%	0.031

While patients in cohort #2 had fewer amputations, nevertheless, they reported a higher rate of adverse physical and psychological outcomes than cohort #1. To start, patients who received amputations within cohort #2 were found to have higher rates of chronic stump infection, non-healing wounds, and phantom limb pain when compared to cohort #1 (Specific Aim 2 – Table 2). Individuals in cohort #2 also reported a higher percentage of any complication after their injury, which included pulmonary embolism, neuropathy, and paresthesia. At 5-years after injury, patients in cohort #2 also reported a higher number of physical and mental health conditions than participants in cohort #1 (Specific Aim 2 – Table 2). Cohort #2 had a higher prevalence of physical ailments including cardiac disease, obstructive sleep apnea, insomnia, headaches, and pain in multiple body locations (limb pain, joint pain, neck pain, and back pain). As such, it is not surprising to see individuals in cohort #2 were more likely to demonstrate long-term opioid use and substance abuse after their injury than those in cohort #1. Finally, patients in cohort #2 were more likely to be diagnosed with a mental health condition, including anxiety, depression, and suicide after injury.

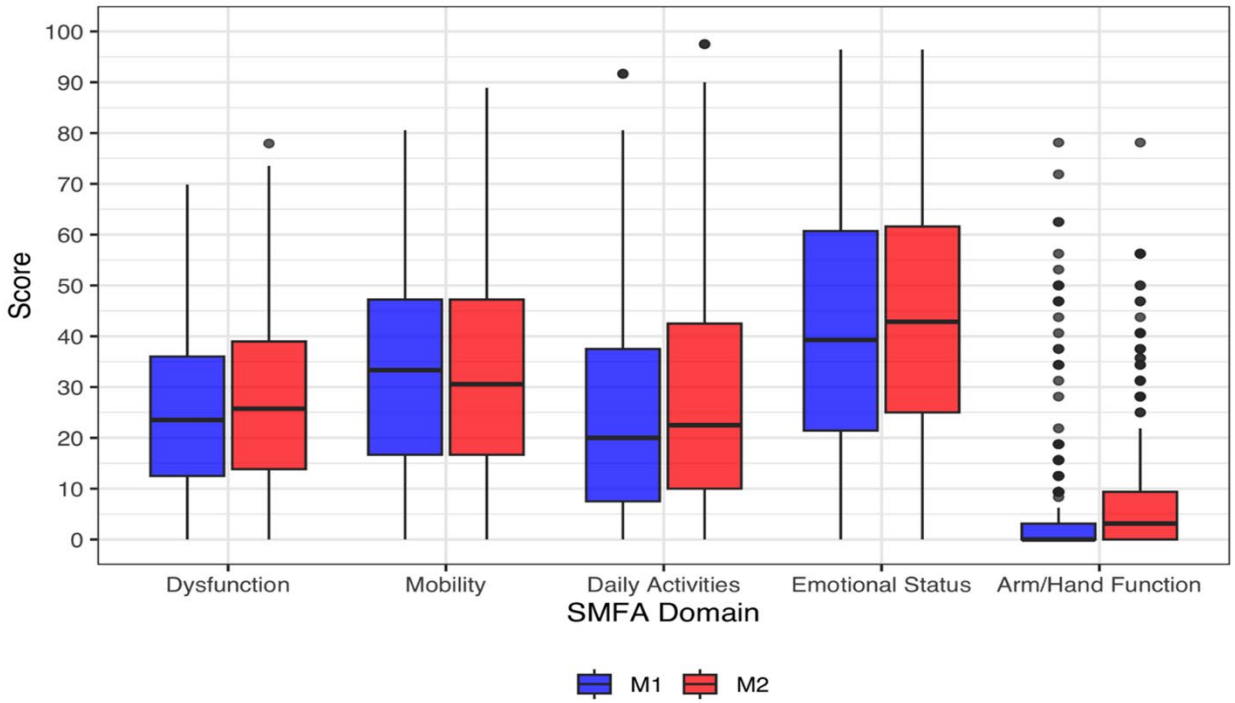
Specific Aim 2 - Table 2: Comparison of Return to Work, Pain and Mental Health Outcomes among Patients in METALS I & METALS II Cohorts

Variables	METALS I – Cohort	METALS II – Cohort	P-value
	(n=324)	(n=288)	
RETURN TO WORK/ACTIVE DUTY			
Return to Work or Active Duty	43.70%	46.30%	0.515
PAIN & MENTAL HEALTH (MH)			
Pain Interference	19.90%	23.70%	0.276
Pain Intensity (Average past 4wks)	4.7 (2.4)	4.4 (2.3)	0.226
Depressed Mood	38.30%	32.60%	0.152
PROMIS Depression	50.8 (12.6)	53.9 (10.5)	0.001
Possible PTSD	20.00%	17.00%	0.404
Possible Depression or PTSD	39.80%	34.00%	0.154
MENTAL HEALTH USE & NEED			<0.001

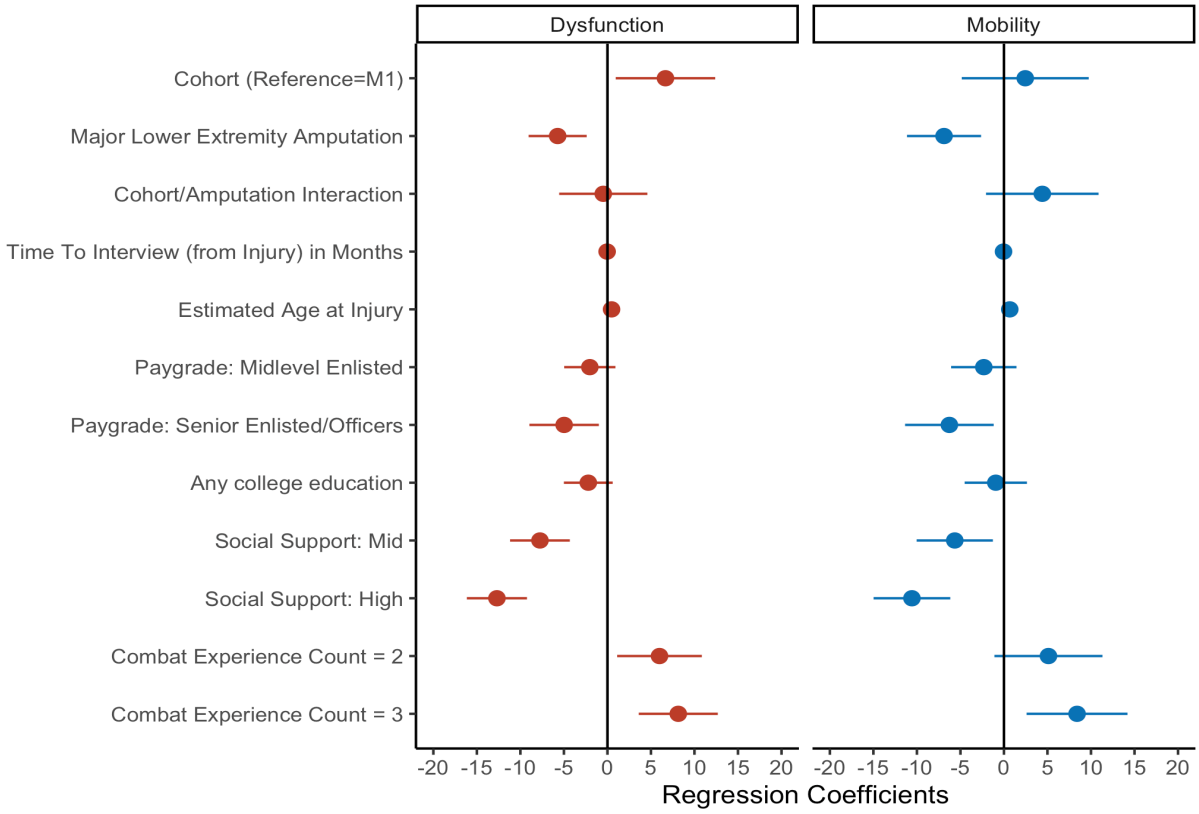
NO, did not need services	56.10%	63.50%	
NO, needed services	4.70%	9.00%	
YES, did not need more services	18.10%	16.30%	
YES, needed more services	21.20%	11.10%	
PT/OT USE & NEED			<0.001
NO, did not need services	40.20%	64.30%	
NO, needed services	10.30%	9.40%	
YES, did not need more services	30.50%	12.90%	
YES, needed more services	19.00%	13.30%	

Comparison of the SMFA domains between the cohorts found very few differences (Specific Aim 2- Figure 1). However, results of the linear regression showed that study participants from M2 had more dysfunction than those in M1, adjusting for all other variables. Increased social support and more seniority were associated with reduced dysfunction and improved mobility, while combat experience was found to be associated with worse outcomes (Specific Aim 2- Figure 2).

Specific Aim 2 – Figure 1: SMFA Domain Scores between METALS I and METALS II Cohorts



Specific Aim 2 – Figure 2: SMFA Linear Regression Outcomes



In summary, we found that individuals who suffered a major limb injury in combat during 2008–2013 were more likely to undergo limb salvage than subjects injured during earlier military campaigns between 2003-2007. However, individuals in this more contemporary cohort were more likely to report major complications as well as be diagnosed with adverse physical and mental health conditions that may be attributed to trauma up to five years after their injury. These findings were sustained even after controlling for demographic characteristics and pre-injury characteristics (adjusted OR 1.13; 1.07-1.19). Relative to participants injured in the earlier period of the Global War on Terror, participants injured between 2008 and 2013 experienced a significant increase in amputation-related complications and diminished functional outcomes. Considerable long-term disability continues to afflict those who suffer major combat-related limb injuries. These findings are contrary to our hypothesis that the later cohort wound have improved psychological and functional outcomes when compared to the earlier patient cohort. We plan to undertake additional risk-adjusted analyses to confirm these findings among different patient groups based on whether they underwent amputation or limb salvage following injury. Full results and methods will be reported in a manuscript which is under preparation.

Specific Aim 3: Examine the incidence of short- & long-term complications following major limb trauma.

All subjects with qualifying injuries were included in this analysis. Certain physical and mental health diagnoses were selected based on precedent literature to determine if frequencies of these

diagnoses were difference between subjects based on limb status (any limb amputation versus limb reconstruction). The diagnoses were determined using health system data from the Department of Defense Military Data Repository and Veterans Health Administration based on ICD-9-CM codes assigned at two or more visits at least seven days apart of assigned to one inpatient diagnosis based on published methodology. We focused on the five-year time span following injury. Comparisons of diagnoses were conducted using chi-square analyses then adjusted for demographics and baseline mental health diagnoses using logistic regression

Major findings include that demographics (age, sex, race, enlisted ranks, and active military component) were similar between subjects with amputations and subjects with limb reconstruction. Pre-injury diagnoses for depression, anxiety, PTSD, TBI, and substance use disorder were also no different.

Specific Aim 3 Table 1: Univariate comparison of frequencies of complications [percent (number)] within 5 years of injury

	Limb Status		
	Limb Reconstruction (n=763)	**Amputation (n=739)**	
Infectious Complications			
SEPTICEMIA	7.34 (56)	11.77 (87)	p=0.0034
INFECTION DUE TO DEVICE	20.84 (159)	17.05 (126)	p=0.0612
CHRONIC STUMP INFECTION	6.95 (53)	25.58 (189)	p<0.0001
OSTEOMYELITIS	29.75 (227)	31.66 (234)	p=0.4215
CELLULITIS	35.26 (269)	40.87 (302)	p=0.0251
POSTOP INFECTION	33.29 (254)	34.51 (255)	p=0.6185
ANY INFECTION	58.06 (443)	67.93 (502)	p<0.0001
Other Complications			
PULMONARY EMBOLISM	14.29 (109)	21.24 (157)	p=0.0004
NONUNION FRACTURES	30.28 (231)	14.61 (108)	p<0.0001
NONHEALING WOUND	17.30 (132)	16.10 (119)	p=0.5341
NEUROPATHY	64.35 (491)	77.00 (569)	p<0.0001
PARESTHESIAS	27.13 (207)	19.89 (147)	p=0.0010
ANY COMPLICATION	88.20 (673)	93.37 (690)	p=0.0006

Contrary to our hypothesis, frequencies of several complications were higher in subjects with amputations. (Table 1) Subjects with limb reconstruction did experience higher frequencies of fracture nonunion and paresthesias. However, when adjusted comparisons between limb status and association with any complications at 1 and 5 years after injury were performed, no differences at 5 years were identified. Compared to M1 patients with amputations, M1 patients with limb reconstruction did experience a higher odds of any complication (aOR 1.5 [95%CI 1.2-2.0]). Patients of Black and Other race/ethnicity experienced higher odds of any complication at

5 years compared to White patients. Baseline depression was also associated with a nearly 3 times higher odds of complications at 5 years (aOR 2.9 [95% CI 1.1-7.8]).

Specific Aim 3, Table 2

	Any Complication within 1 year after injury		Any Complication within 5 years after injury	
	aOR	**(95% CI)**	**aOR**	**(95% CI)**
Study Groups				
M1: Amputation (Ref)				
M1: Limb Salvage	1.513	(1.156-1.98)	0.718	(0.513-1.005)
M2: Amputation	0.437	(0.296-0.645)	0.957	(0.604-1.516)
M2: Limb Salvage	0.917	(0.677-1.241)	1.029	(0.694-1.525)
Age In Year of Injury				
	1.007	(0.987-1.028)	1.019	(0.994-1.044)
Race-Ethnicity				
White (Ref)				
Asian	1.405	(0.977-2.028)	0.788	(0.467-1.274)
Black	0.754	(0.517-1.095)	1.585	(1.023-2.409)
Hispanic	0.951	(0.668-1.353)	1.288	(0.832-1.951)
Other	1.536	(0.747-3.207)	2.335	(1.065-4.829)
Branch				
Army (Ref)				
Air Force	1.227	(0.547-2.842)	1.99	(0.835-4.404)
Marines	1.194	(0.895-1.596)	0.996	(0.685-1.429)
Navy/Cg	1.121	(0.53-2.431)	1.281	(0.497-2.904)
Unknown	0.299	(0.117-0.689)	0.901	(0.323-2.158)
Rank				
Enlisted (Ref)				
Officer/Warrant	1.232	(0.805-1.893)	1.147	(0.689-1.852)
Component				
Active (Ref)				
Guard/Reserve	1.084	(0.81-1.452)	0.829	(0.561-1.203)
Unknown	1.035	(0.529-2.058)	0.442	(0.129-1.141)
Sex				
Male (Ref)				
Female	1.054	(0.525-2.114)	0.926	(0.359-2.094)
Marital Status				
Married (Ref)				
Unmarried	0.972	(0.775-1.22)	0.784	(0.587-1.043)
Mental Condition				
Baseline Anxiety	1.759	(0.521-6.883)	2.512	(0.7-8.089)
Baseline Depression	2.886	(0.988-9.916)	2.913	(1.065-7.78)

Baseline PTSD	1.132	(0.272-5.832)	0.35	(0.046-1.647)
Baseline Substance Use Disorder	1.344	(0.682-2.746)	1.675	(0.789-3.353)
TBI in Year of Injury				
	4.628	(3.323-6.555)	0.957	(0.656-1.375)

aOR, Adjusted Odds Ratio; CI, Confidence Intervals

Among health conditions, subjects with amputations experienced more cardiac diagnoses and phantom limb pain while subjects with limb reconstruction experienced more joint pain/osteoarthritis, headache, and alcohol use disorder. The remaining physical and mental conditions were not different based on limb status.

Specific Aim 3 Table 3: Comparison of frequencies of diagnoses [percent (number)] within 5 years of injury

	Limb Status		
	Limb Reconstruction (n=763)	**Amputation (n=739)**	
Physical Health Diagnoses			
LIMB PAIN	76.28 (582)	76.28 (564)	p=0.9849
JOINT PAIN	82.18 (627)	63.19 (467)	p<0.0001
OSTEOARTHRITIS	14.02 (107)	7.98 (59)	p=0.0002
NECK PAIN	13.37 (102)	14.34 (106)	p=0.5843
BACK PAIN	51.64 (394)	48.85 (361)	p=0.2799
LUNG DISEASE	3.80 (29)	3.25 (24)	p=0.5613
CARDIAC	19.53 (149)	24.63 (182)	p=0.0171
DIABETES	2.88(22)	3.25 (24)	p=0.6821
HBP	14.55 (111)	15.97 (118)	p=0.4441
OBESITY	21.23 (162)	18.67 (138)	p=0.2151
STROKE/CVD	6.68 (51)	4.87 (36)	p=0.1327
OSA	12.32(94)	10.42 (77)	p=0.2464
INSOMNIA	48.62(371)	48.04 (355)	p=0.8203
HEADACHE	33.81(258)	26.93(199)	p=0.0037
Mental Health Diagnoses			
ANXIETY	39.19 (299)	32.88(243)	p=0.110
DEPRESSION	38.40(293)	37.35 (276)	p=0.6740
PTSD	64.35 (491)	60.22 (445)	p=0.0983
OPIOID USE DISORDER	8.65 (66)	6.50 (48)	p=0.1149
ALCOHOL USE DISORDER	17.43 (133)	13.53 (100)	p=0.0369
OTHER SUBSTANCE USE	27.26 (208)	23.41 (173)	p=0.0864
SUICIDE	5.24 (40)	4.47 (33)	p=0.4839
OVERDOSE	13.24 (101)	12.58 (93)	p=0.7061
LONG-TERM OPIOID USE	55.31 (422)	55.35 (409)	p=0.9885

To focus long-term opioid use, no differences were identified in odds of long term use based on limb status at 1 and 5 years after injury (Table 4). TBI at the time of injury was associated with opioid use at 1 year following injury but this did not continue to be associated at the 5 year post injury mark.

Specific Aim 3, Table 4

	Long Term Opioid Use within 1 year after injury		Long Term Opioid Use within 5 years after injury	
	aOR	**(95% CI)**	**aOR**	**(95% CI)**
Study Groups				
M1: Amputation (Ref)				
M1: Limb Salvage	0.939	(0.662-1.333)	0.843	(0.586-1.214)
M2: Amputation	0.896	(0.585-1.373)	1.222	(0.728-2.051)
M2: Limb Salvage	0.986	(0.677-1.437)	0.809	(0.544-1.203)
Age In Year of Injury				
	1.006	(0.981-1.031)	1.003	(0.976-1.03)
Race-Ethnicity				
White (Ref)				
Asian	1.352	(0.877-2.047)	1.017	(0.624-1.606)
Black	0.445	(0.241-0.768)	1.029	(0.618-1.649)
Hispanic	0.82	(0.512-1.271)	0.689	(0.401-1.128)
Other	0.812	(0.294-1.909)	0.848	(0.282-2.08)
Branch				
Army (Ref)				
Air Force	2.078	(0.881-4.628)	1.157	(0.378-2.921)
Marines	1.04	(0.723-1.48)	0.974	(0.657-1.422)
Navy/Cg	0.917	(0.353-2.092)	1.834	(0.752-4.047)
Unknown	1.281	(0.489-2.982)	0.494	(0.078-1.729)
Rank				
Enlisted (Ref)				
Officer/Warrant	1.037	(0.62-1.683)	0.195	(0.059-0.479)
Component				
Active (Ref)				
Guard/Reserve	0.692	(0.459-1.019)	0.943	(0.628-1.388)
Unknown	1.526	(0.721-3.041)	0.459	(0.109-1.312)
Sex				
Male (Ref)				
Female	2.15	(0.951-4.532)	0.509	(0.12-1.476)
Marital Status				
Married (Ref)				
Unmarried	0.824	(0.621-1.091)	0.98	(0.725-1.322)
Mental Condition				

Baseline Anxiety	1.721	(0.473-5.603)	0.367	(0.02-1.977)
Baseline Depression	2.315	(0.847-6.177)	1.363	(0.383-4.108)
Baseline PTSD	0.454	(0.06-2.102)	0.893	(0.116-4.511)
Baseline Substance Use Disorder	2.208	(1.108-4.267)	1.896	(0.868-3.869)
TBI in Year of Injury				
	2.306	(1.672-3.17)	0.844	(0.562-1.243)

aOR, Adjusted Odds Ratio; CI, Confidence Intervals

In summary, we found that complications and diagnoses identified up to five years follow injury were largely not different between subjects with amputation and with limb reconstruction. There were notable exceptions where subjects with amputations specifically experienced more infection complications and cardiac conditions, contrary to our hypotheses. Additional analyses may be undertaken with the full merged analytical file where these complications and conditions can be tested for associations with self-reported functional outcomes in subjects who completed the interview in Aims 1 and 2. Full results and methods will be reported in a manuscript which is under preparation.

Specific Aim 4: Examine short- and long-term use of medical, mental health and rehabilitation services and compare rates of use between amputees and limb salvage patients in Cohorts #1 and #2.

Between the injury time periods for Cohort 1 and 2 occurred the expansion of rehabilitation options for patients undergoing limb reconstruction. Anecdotal experience suggests that amputation care centers being available to service members injured during earlier years of conflict may contribute to differences in outcomes identified in the METALS 1 study. As a result, we aimed to determine if the METALS 2 (Cohort 2) subjects did access services at differential rates, particularly for subjects undergoing limb reconstruction. Applying methods similar to those employed in Aim 3, Department of Defense Military Data Repository and Veterans Health Administration data were used to identify clinic codes of interest representing access to health care services. The frequency of care services utilization was them compared between cohorts.

We identified that several types of clinic utilization did increase for Cohort 2 compared to Cohort 1. No utilization decreased in these comparisons. Utilization of Audiology, Cardiology, Primary Care, Substance Abuse, and Vascular Surgery Clinics were not different between time frames.

For clinic utilization where Cohort differences were identified, additional chi-square analyses attempted to determine limb status difference therein contributed to the time frame differences. In SA4, Table 1, the percent and number of subjects accessing the various clinics are presented. Among Cohort 1 Amputation subjects, Cohort 1 Limb Reconstruction subjects, Cohort 2 Amputation subjects, and Cohort 2 Limb Reconstruction subjects, the group result that most

contributes to the Chi-square outcome (cell Chi-square) is highlighted, indicating the groups where the expected and observed result most diverges in the chi-square analyses.

Specific Aim 4 Table 1: Clinic Utilization frequencies between subjects in Cohort 1 and Cohort 2 [percent (number)] and limb status breakdown (percent) 5 years after injury

	M1 Cohort (n=966)		M2 Cohort (n=536)		
	A	LR	A	LR	
ALLERGY/IMMUNOLOGY CLINIC	42.13 (407)		56.53 (303)		p<0.0001
	47.68	35.13	58.50	55.36	
EMERGENCY DEPARTMENT	87.27 (843)		90.86 (487)		p=0.0363
	86.83	87.82	91.00	90.77	
ENT CLINIC	37.89 (366)		49.25 (264)		p<0.0001
	38.03	37.70	54.50	46.13	
MENTAL HEALTH CARE CLINIC	96.17 (929)		99.81 (535)		p<0.0001
	98.52	93.21	100	99.70	
NEUROLOGY CLINIC	59.21 (572)		94.22 (505)		p<0.0001
	60.48	57.61	97.00	92.56	
ORTHO/SPINE/ AMPUTATION	97.00 (937)		99.81 (535)		p=0.0002
	98.89	94.61	100	99.70	
PAIN CLINIC	39.13 (378)		86.57 (464)		p<0.0001
	40.07	37.94	87.00	86.31	
PULMONARY CLINIC	20.39 (197)		46.46 (249)		p<0.0001
	22.08	18.27	47.00	46.13	
PMR CLINIC	76.60 (740)		95.34 (511)		p<0.0001
	91.84	57.38	99.50	92.86	
PT/OT CLINIC	96.17 (929)		99.81 (535)		p<0.0001
	98.70	92.97	100	99.70	
SPEECH PATHOLOGY CLINIC	25.67 (248)		51.49 (276)		p<0.0001
	30.61	19.44	58.50	47.32	
SURGERY CLINIC	94.51 (913)		100 (536)		p<0.0001
	93.69	95.55	100	100	

A=Amputation Subjects; LR=Limb Reconstruction Subjects

Further consideration of mental health and pain utilization is notable for a few points. The second cohort had higher frequencies of pre-injury depression (1.04 v 2.61%; p=0.0196), anxiety (0.52 v 1.68%; p=0.0245), PTSD (0.41 v 1.49%; p=0.0245), and substance use disorder (1.24 v

6.16%; p<0.0001). This timeframe effect is accentuated in the frequencies of all studied mental health diagnoses except for PTSD and including prolonged opioid use.

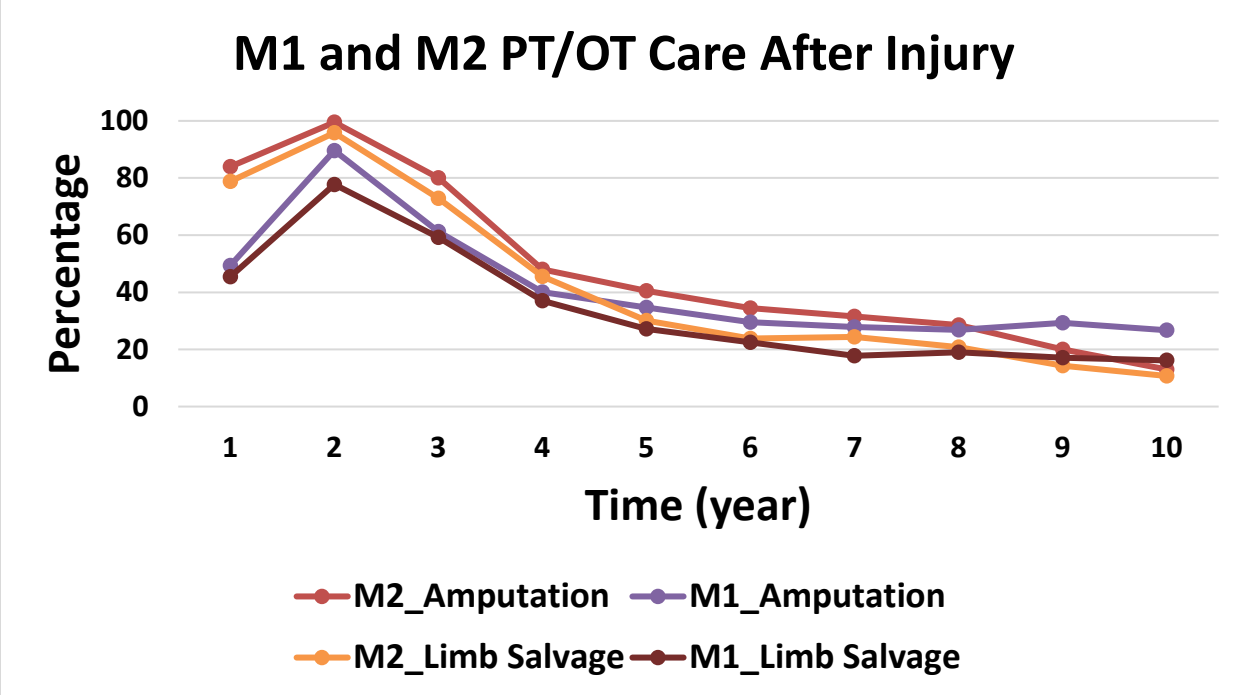
To address our hypotheses we focused exclusively on PT/OT and Mental Health Care utilization.

a. Use of PT/OT and mental health services would be lower for those undergoing limb salvage vs. amputation.
b. For limb salvage patients, use of PT/OT and mental health services would be higher for those in Cohort #2 compared to Cohort #1.

Based on our existing work with traumatic brain injury, we also hypothesized that those who had TBI documented during the year of injury would be more likely to have mental health care 5 and 10 years after injury.

Aim 4 Figure 1 provides utilization of PT/OT over time in years after injury for individuals in each study group (Cohort 1 Amputation, Cohort 1 Limb Salvage, Cohort 2 Amputation, Cohort 2 Limb Salvage). As one might expect, utilization of PT/OT was more common early in the course of treatment and peaked for all groups two years after injury. Utilization was higher for Cohort 2 vs. Cohort 1 through year 4 after which the Cohort 2 limb salvage group was similar to the Cohort 1 limb salvage group. Between years 5 and 7, the Cohort 2 amputation group continued to have higher use of PT/OT care compared to the Cohort 1amputation group. After that (when it was unlikely that data were available for most of the Cohort 2 amputation group), the Cohort 1 amputation group had the highest use of PT/OT.

Aim 4 Figure 1: Annual PT/OT Use Each Year After Injury



Multivariable logistic regression models further evaluated differences between study groups on PT/OT utilization controlling for sociodemographic and military characteristics in Model 1 and adding covariates for mental health conditions diagnosed prior to injury, and TBI diagnosis at the time of injury. In both models, Cohort 1 members with limb salvage were more likely to continue to receive PT/OT 5-years after injury than those who sustained an amputation, but there was not a significant difference between the limb salvage cohorts (aOR 0.87 [0.62-1.22). Moreover, there was no difference in the extent to which individuals with amputation remained in PT/OT based cohort Cohort 1 vs. Cohort 2. Examining covariates, we found that those who were injured at an older age were more likely to receive PT/OT 5 years after injury than those who were injured younger. Those who served in the Air Force and those who served in the National Guard/Reserve were significantly less likely to receive PT/OT 5 years after injury than those who served in the Army and Active Duty component respectfully. None of the clinical characteristics were significantly associated with continued PT/OT care at 5 years.

Specific Aim 4: Table 2
Logistic Regression Predicting Use of OT/PT 5 Years after Injury

	Physical Therapy/Occupational therapy use 5 years after injury			
	aOR	**(95% CI)**	**aOR**	**(95% CI)**
Study Groups				
M1: Amputation (Ref)				
M1: Limb Salvage	**1.43**	**(1.07-1.90)**	**1.42**	**(1.07-1.89)**
M2: Amputation	0.73	(0.52-1.03)	0.75	(0.52-1.06)
M2: Limb Salvage	1.21	(0.90-1.65)	1.22	(0.89-1.66)
Age In Year of Injury				
	1.04	**(1.02-1.06)**	**1.04**	**(1.02-1.06)**
Race-Ethnicity				
White (Ref)				
Asian	1.11	(0.76-1.61)	1.10	(0.75-1.60)
Black	1.37	(0.94-1.98)	1.38	(0.95-1.99)
Hispanic	1.42	(1.00-2.01)	1.44	(1.01-2.04)
Other	2.04	(1.01-4.07)	2.02	(1.00-4.04)
Branch				
Army (Ref)				
Air Force	**0.40**	**(0.13-0.98)**	**0.39**	**(0.13-0.98)**
Marines	1.25	(0.93-1.66)	1.26	(0.94-1.68)
Navy/Coast Guard	1.55	(0.75-3.12)	1.59	(0.77-3.22)
Rank				
Enlisted (Ref)				
Officer/Warrant	1.08	(0.71-1.64)	1.09	(0.71-1.64)
Component				

Active (Ref)				
Guard/Reserve	**0.70**	**(0.51-0.96)**	**0.71**	**(0.52-0.97)**
Sex				
Male (Ref)				
Female	1.40	(0.69-2.78)	1.39	(0.68-2.77)
Marital Status				
Married (Ref)				
Unmarried	1.00	(0.79-1.26)	1.00	(0.79-1.25)
Mental Health Diagnoses Before Injury				
Anxiety			0.85	(0.22-2.76)
Depression			1.48	(0.55-3.89)
PTSD			0.32	(0.05-1.40)
Substance Use Disorder			1.34	(0.69-2.54)
TBI In Year of Injury			1.02	(0.76-1.36)

aOR, Adjusted Odds Ratio; CI, Confidence Intervals

We examined 10 year utilization outcomes for individuals in the M1 Cohort and found that those with amputation were significantly more likely to continue with PT/OT utilization compared to those with limb salvage. Similar to the 5 year analysis, those who were injured at an older age were more likely to receive PT/OT 10 years after injury. At 10 years post-injury those who were unmarried were less likely to receive PT/OT care.

Specific Aim 4: Table 3
Logistic Regression Predicting Use of OT/PT 10 Years after Injury: Cohort 1 Only

	Physical Therapy/Occupational therapy 10 years after injury	
	aOR	**(95% CI)**
Study Groups		
M1: Limb Salvage (Ref)		
M1: Amputation	**1.93**	**(1.39-2.7)**
Age In Year of Injury		
	1.03	**(1.01-1.06)**
Race-Ethnicity		
White (Ref)		
Asian	1.19	(0.72-1.93)
Black	1.07	(0.64-1.76)
Hispanic	0.81	(0.46-1.37)
Other	0.91	(0.25-2.57)
Branch		

Army (Ref)		
Air Force	0.47	(0.07-1.78)
Marines	0.85	(0.56-1.26)
Navy/CG	1.52	(0.60-3.66)
Rank		
Enlisted (Ref)		
Officer/Warrant	1.4	(0.79-2.42)
Component		
Active (Ref)		
Guard/Reserve	0.82	(0.54-1.21)
Sex		
Male (Ref)		
Female	1.01	(0.35-2.55)
Marital Status		
Married (Ref)		
Unmarried	**0.65**	**(0.47-0.91)**
Mental Health Diagnoses Before Injury		
Anxiety	1.22	(0.06-9.10)
Depression	0.75	(0.08-4.28)
PTSD	1.31	(0.05-18.24)
Substance Use Disorder	0.68	(1.00-2.88)
TBI In Year of Injury		
	1.44	(0.88-2.28)

These findings were partially supportive of our hypotheses for PT/OT utilization. Our hypothesis was not supported at the 5-year point where those with limb salvage (from both cohorts) were more like to have PT/OT utilization. However, at 10 years, our hypothesis was supported as those with amputation in Cohort 1 were more likely to have PT/OT utilization. This suggests the need for longer-term observation to better understand the impact of these distinct orthopedic injuries.

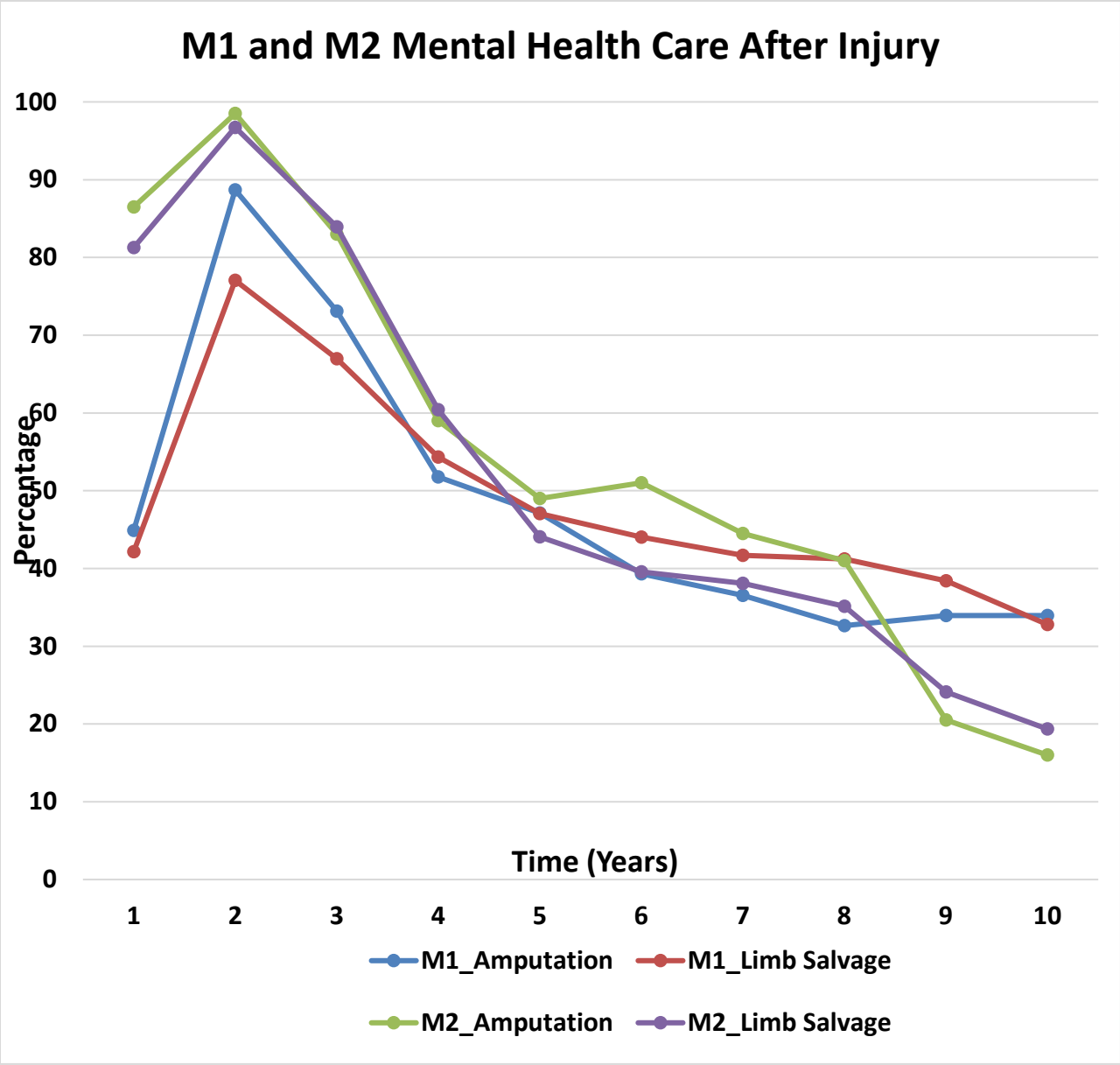
Mental Health Service Utilization

Figure 2 (Aim 4) provides utilization of any mental health care over time in years after injury for individuals in each study group (Cohort 1 Amputation, Cohort 1 Limb Salvage, Cohort 2 Amputation, Cohort 2 Limb Salvage). Similar to PT/OT, utilization for mental health was high in the year of injury and peaked the second year after injury. Utilization was higher for Cohort 2 vs. Cohort 1 cohort through year 4 after which utilization for the Cohort 2 limb salvage group was lower than other groups almost consistently through year 8 when data for Cohort 2 becomes sparse.

Multivariable logistic regression models further evaluated differences between study groups on mental health care utilization controlling for sociodemographic and military characteristics in Model 1 and adding covariates for mental health conditions diagnosed prior to injury, and TBI

diagnosis at the time of injury. In both models, there were no significant differences among any of the Cohort 1/ Cohort 2 amputation/limb salvage groups 5 years after injury. Examining covariates, we found that those who were injured at an older age were more likely to receive mental health care 5 years after injury than those who were younger at the time of injury. Women were more also likely to receive mental health care 5 years after injury than men. None of the clinical characteristics including mental health diagnoses before injury were significantly associated with continued mental health care at 5 years.

Aim 4 Figure 2: Mental Health Care Utilization After Injury



Specific Aim 4: Table 4
Logistic Regression Predicting Use of Mental Health Care 5 Years after Injury

	Mental Health Care 5 Years After Injury			
	aOR	**(95% CI)**	**aOR**	**(95% CI)**
Study Groups				
M1: Amputation (Ref)				
M1: Limb Salvage	0.97	(0.75-1.26)	0.98	(0.75-1.27)
M2: Amputation	0.86	(0.62-1.20)	0.80	(0.56-1.12)
M2: Limb Salvage	1.09	(0.82-1.44)	1.04	(0.77-1.39)
Age In Year of Injury				
	1.02	(1.00-1.04)	1.02	(1.00-1.04)
Race-Ethnicity				
White (Ref)				
Asian	1.11	(0.78-1.57)	1.09	(0.77-1.55)
Black	1.38	(0.97-1.98)	1.41	(0.98-2.01)
Hispanic	1.32	(0.94-1.84)	1.28	(0.91-1.79)
Other	0.73	(0.35-1.46)	0.73	(0.35-1.46)
Branch				
Army (Ref)				
Air Force	0.71	(0.33-1.51)	0.70	(0.32-1.50)
Marines	1.03	(0.78-1.35)	1.09	(0.83-1.43)
Navy/Coast Guard	0.84	(0.41-1.67)	0.91	(0.44-1.83)
Rank				
Enlisted (Ref)				
Officer/Warrant	0.73	(0.48-1.08)	0.74	(0.49-1.11)
Component				
Active (Ref)				
Guard/Reserve	1.06	(0.80-1.40)	1.05	(0.79-1.40)
Unknown	0.92	(0.48-1.72)	0.91	(0.48-1.72)
Sex				
Male (Ref)				
Female	**2.37**	**(1.19-5.0)**	**2.27**	**(1.13-4.81)**
Marital Status				
Married (Ref)				
Unmarried	0.98	(0.79-1.21)	1.00	(0.8-1.24)
Mental Health Diagnoses Before Injury				
Anxiety			2.09	(0.65-7.97)
Depression			1.90	(0.72-5.38)
PTSD			2.22	(0.56-11.06)
Substance Use Disorder			1.30	(0.69-2.47)
TBI In Year of Injury				

	0.64	**(0.48-0.84)**

aOR, Adjusted Odds Ratio; CI, Confidence Intervals

We examined 10 year mental health utilization outcomes for individuals in Cohort 1 and found no difference in mental health care utilization between limb salvage and amputation groups. Military characteristics were associated with mental health care 10 years after injury. Navy/Coast Guard members and officers/warrant officers were less likely than those from the Army and enlisted members respectively to receive mental health care in year 10. Finally, contrary to our hypothesis, mental health care was less likely among individuals with a TBI diagnosed during the year of injury.

Specific Aim 4: Table 5
Logistic Regression Predicting Use of Mental Health Care 10 Years after Injury: M1 Cohort Only

	Mental Health Care 10 years after injury	
	aOR	**(95% CI)**
Study Groups		
M1: Limb Salvage (Ref)		
M1: Amputation	1.04	(0.79-1.38)
Age In Year of Injury		
	1.02	(1-1.05)
Race-Ethnicity		
White (Ref)		
Asian	0.70	(0.44-1.08)
Black	1.00	(0.64-1.55)
Hispanic	0.73	(0.45-1.14)
Other	0.58	(0.2-1.45)
Branch		
Army (Ref)		
Air Force	**0.22**	**(0.03-0.87)**
Marines	0.83	(0.59-1.16)
Navy/Cg	**0.31**	**(0.09-0.88)**
Unknown	0.68	(0.21-1.87)
Rank		
Enlisted (Ref)		
Officer/Warrant	**0.55**	**(0.31-0.94)**
Component		
Active (Ref)		

Guard/Reserve	**0.69**	**(0.49-0.98)**
Unknown	1.65	(0.56-4.76)
Sex		
Male (Ref)		
Female	1.82	(0.78-4.21)
Marital Status		
Married (Ref)		
Unmarried	1.03	(0.77-1.36)
Mental Condition		
Baseline Anxiety	2.31	(0.34-19.34)
Baseline Depression	2.73	(0.58-15.38)
Baseline PTSD	1.70	(0.12-20.65)
Baseline Substance Use Disorder	0.45	(0.09-1.69)
TBI In Year of Injury		
	0.66	(0.41-1.04)

aOR, Adjusted Odds Ratio; CI, Confidence Intervals

These findings partially supported our hypotheses. Early in care, individuals with limb salvage were less likely to use mental health care, with the finding stratified by Cohort. Cohort 1 had lower mental health care utilization in years 1-4 than cohort two, and in each cohort those with limb salvage had lower mental health care utilization than those with amputation. Multivariable models found no difference among the groups. Furthermore, we found that those with TBI the year of injury were less likely to have mental health care 10 years after injury.

Considering our hypotheses, these data support our notion that differences existed in the M1 Cohort between subjects with amputations and subjects with limb reconstruction as evidenced here by lower frequencies of Mental Health, Orthopaedic, PM&R, and PT/OT clinic utilization compared to the other sub-cohorts. Health care utilization increased overall, though, for the entire M2 Cohort regardless of limb status. Full results and methods will be reported in a manuscript which is under preparation.

5.4 Strengths and Weaknesses of Current Study

This study has several strengths including ability to link to prior cohort and compare results within and across cohorts, as well as the use of well-established measures to assess functional status as well as the likelihood of depression and PTSD.

As with any observational study, however, limitations exist that must be taken into account when interpreting the results. First, for cohort 2, this is a cross sectional study, and the time to interview did not match the time to interview for cohort 1 (time to interview). While time to injury was considered in the analysis, the lack of a prospective design and a uniform timing of the outcome assessment limit our ability to establish causal relationships.

The lack of detailed clinical data on cohort 2 impaired our ability to characterize the injuries that resulted in amputation, and may be responsible for some of the differences in distribution of

injuries. Thus we cannot directly compare the factors associated with the propensity for amputation, although the assumption that injuries leading to amputation are likely to be as or more severe than those resulting in limb salvage is likely appropriate, and can be used to frame the interpretation of study results.

Our response rate to the survey was modest (61%) although, our analysis of characteristics and utilization patterns of responders and non-responders showed little variation.

Finally, all outcomes are based on self-report. Although the instruments we used to measure overall function and symptoms of depression and PTSD are well established with good psychometric properties, they fall short of providing a diagnosis based on clinical examination. This impact was somewhat mitigated by our ability to look at utilization data for the entire cohort as well as for responders.

5.4 Opportunities for Training and Professional Development

Nothing to report.

5.5 Dissemination of Results

In 2018, a poster was presented at the MHSRS meeting, summarizing the potential impact of selection bias in this population, "Selection Bias in Military Cohort Studies: An Analysis of Differences between Participants and Non-Participants in a Study of Service Members with Severe Limb Trauma." Key dissemination activities are planned for the coming year. Two abstracts were accepted for podium presentation at the 2023 Orthopaedic Trauma Association 2023 meeting, "Changes in Functional Outcomes Over Time Following Major Lower Limb Trauma Among Veterans Undergoing Primary Amputation versus Limb Salvage" and "Changes in Functional Outcomes Over Time Following Major Lower Limb Trauma Among Veterans Undergoing Primary Amputation versus Limb Salvage," and the same two abstracts were accepted as posters at the MHSRS 2023 meeting, the 2023 Limb Lengthening and Reconstruction Society Meeting and any future Extremity War Injuries meeting, as well as major publications covering the primary aims of the study.

The following manuscripts are underway and will be submitted for publication:

1. Functional outcomes (interview data) - METALS I – T1 v T2
2. Functional outcomes (interview data) – METALS I v METALS II
3. Long term complications (utilization data) – M1 and M2, amp v salvage
4. Short and long term utilization of medical, mental health, and rehab svs (utilization data) – M1 and M2, amp v salvage

6. Impact

6.1 Impact on Developing of the Principal Discipline of the Project

While several comparisons between cohort and between subjects depending on limb status are included to address our aims, the overarching and glaring evidence herein is that these patients

with severe limb injuries are in the long term significantly affected with self-reported outcomes markedly worse than population normative values and high, prolonged, health care utilization.

Often orthopaedic surgeons want to know which limb outcomes is "better" as it is reassuring to be able to council patients accordingly. However, surgeons should be cautious with these results unless able to explain that neither amputation nor limb reconstruction returns a patient to pre-injury functional status. It cannot be minimized the seriousness of these irrevocable injuries, regardless of the ultimate limb status.

6.2 Impact on Other Disciplines

Patients who sustain combat injury will have long term sequelae that overlaps with several disciplines. Having a compromised limb, regardless of limb status, affects mobility which in the long term could have implications on many body systems. Pain is a persistent issue which is complex and requires safe, long-term solutions as long term opioid use is not desirable. Mental health care is crucial for this population.

6.3 Impact on Technology Transfer

While no technologies were specifically addressed herein, technological developments intended to improve outcomes following severe injury should be studied for their effects on the types of outcomes used in this study.

The development of a web-based survey and centralized, web-based phone center improved efficiency in this study, and the proportion of respondents who chose the web-based survey (76%) over a telephone interview indicates

6.4 Impact on Society beyond Science and Technology

Combat veterans who sustain a serious injury face a lifespan of consequences, some visible to society (such as a limb amputation) and many invisible (TBI, PTSD, chronic pain, etc). Serious combat injury results in function that is not restored to match the typical young and healthy working aged individual which has personal and societal consequences. Serious limb injuries, however, are not isolated to combat trauma; and civilian patients could conceivably experience a similar challenging road to follow.

7. Changes/Problems

7.1 Changes in Approach and Reasons for Change

Two substantive changes were made to the approach over the course of the study. First, the fifth aim, which proposed to examine the geospatial distribution of participants relative to VA hospitals was not possible due to the departure of an original investigator from the study. Changes to the location and affiliations of our principal investigators (Rivera, Pugh) necessitated the establishment and subsequent revision of extensive protocol and data sharing agreements that

radically slowed the pace of work on this project. We were further challenged by multiple investigator changes at the USAISR, and lacking an investigator sponsor at the ISR, were consequently unable to establish a data sharing agreement with the Joint Trauma System and access MOTR data. The consequence of this change was an inability to obtain detailed injury information on our subjects, and made comparison between cohorts 1 and 2 by amputation status less precise than desired.

Finally, instead of completing a fully qualitative study on changes in practice and recommendations over the period of time when participants were injured, we relied on the clinical expertise of our investigators and protocol committee and literature reviews to provide this perspective on our analysis.

7.2 Actual or Anticipated Problems or Delays and Actions to Resolve Them

Changes to the location and affiliations of our principal investigators (Rivera, Pugh) necessitated extensive protocol and data sharing agreements that radically slowed the pace of work on this project. We were further challenged by multiple investigator changes at the USAISR, where the military sponsor for the JTS data sharing agreement must originate from. The final result was that no sponsor at the USAISR was finalized, and we were not able to submit a request for access to the MOTR data in the JTS system.

7.3 Changes that had a Significant Impact on Expenditures

There were no changes that had impact on expenditures.

7.4 Significant Changes in Use or Care of Human Subjects

No changes were made that impacted care of human subjects.

8. Products

Several manuscripts are being completed at this time and will be submitted in the coming year.The study abstractors were responsible for ensuring the entry of detailed injury and treatment information on all consented METALS 2 participants into the Military Orthopaedic Trauma Registry maintained by the Joint Trauma System, ensuring that these data will be available for future research purposes. The investigators will ensure analytic access to the rich, deidentified, merged dataset created as a part of this study, which includes interview data and time 1 and time 2 for the METALS 1 cohort, interview data for the METALS 2 cohort, and all Veterans Health Administration utilization data for 10 years following injury. These data are available upon presentation and approval of an analytic plan to the Major Extremity Trauma Research Consortium (METRC) publications committee.

9. Participants and Other Collaborating Organizations

Key Personnel:

Name: *Ellen MacKenzie, PhD* *Project Role:* *Principal Investigator* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked:* *1.2 cal months* *Contribution to Project:* *Dr. MacKenzie provides overall study design and oversite on this project.*
Name: *Katherine Frey, RN, MPH* *Project Role:* *Project Director* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked:* *3.0 cal months* *Contribution to Project:* *Ms. Frey provides coordination and analysis of study processes, including the supervising development of the study protocol, and is coordinating the establishment of the MOUs and CRADAs. She will oversee all IRB submissions.*
Name: *Elizabeth Wysocki, MS* *Project Role:* *Study Manager* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked:* *3.6 cal months* *Contribution to Project:* *Ms. Wysocki provides program support to Ms. Frey,, including researching information, setting up the study website, recruiting study interviewers, and developing procedures for data transfer and subject follow-up.*
Name: *Manish Anand, MBA* *Project Role:* *Finance Manager* *Researcher ID* *NA* *Nearest person month worked:* *0.6 cal months* *Contribution to Project:* *Manages the pre-award and post-award activities including the financials for the study.*
Name: *Joseph Wenke, MD* *Project Role:* *Co-Investigator* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked:* *0.6 cal months* *Contribution to Project:* *Dr. Wenke is responsible for overall oversight on this project at the Institute for Surgical Research.*
Name: *Benjamin Potter, MD* *Project Role:* *Co-Investigator* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked:* *0.6 cal months* *Contribution to Project:* *Dr. Potter is responsible for overall oversight on this project at WRNMMC.*
Name: *Jessica Rivera, PhD* *Project Role:* *Co-Investigator* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked:* *1.51 cal months*

Contribution to Project: Dr. Rivera served as the study Co-PI and was the ISR principal investigator from 2015-2018, when she retired from the military.
Name: Mary Jo Pugh, PhD *Project Role: Co-Investigator* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked: 1.51 cal months* *Contribution to Project: Dr. Pugh was at UTHSA till November 2017 and moved to Utah. She is responsible for data coordination at Utah currently.*
Name: Benjamin Brooke MD, PhD *Project Role: Site Co-Investigator* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked: 0.48 cal months* *Contribution to Project: Dr. Brooke is a vascular surgeon responsible for providing clinical input related to limb reconstruction and subsequent outcomes.*
Name: Megan Amuan MPH *Project Role: Data Manager/analyst* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked: .5 cal months* *Contribution to Project: Ms. Amuan is responsible for data compilation and coordination at Utah and analyses of health system data.*
Name: Jared Hansen MStat *Project Role: Data Analyst* *Researcher Identifier (e.g. ORCID ID): N/A* *Nearest person month worked: 1 cal. months* *Contribution to Project: Mr. Hansen (Utah) developed analytic data sets for analysis of Aims 1 and 2 assisting Dr. Brooke with analysis and manuscript preparation.*

Collaborating Organizations

The following institutions provided access to patients per their local IRB approvals and certification by the Coordinating Center:

US Institute for Surgical Research at San Antonio Military Medical Center

Walter Reed National Military Medical Center

Veterans Affairs/University of Utah Health Science Center at Salt Lake City

10. Special Reporting Requirements

N/A

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