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Methodology of AA CRASH: a prospective observational study evaluating the incidence and pathogenesis of adverse post-traumatic sequelae in African-Americans experiencing motor vehicle collision

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ABSTRACT

Introduction: A motor vehicle collision (MVC) is one of the most common life-threatening events experienced by individuals living in the USA. While most individuals recover following MVC, a significant proportion of individuals develop adverse post-traumatic sequelae such as post-traumatic stress disorder or persistent musculoskeletal pain. Adverse post-traumatic sequelae are common, morbid and costly public health problems in the USA and other industrialised countries. The pathogenesis of these disorders following MVC remains poorly understood. In the USA, available data suggest that African-Americans experience an increased burden of adverse post-traumatic sequelae after MVC compared to European Americans, but to date no studies examining the pathogenesis of these disorders among African-Americans experiencing MVC have been performed.

Methods and analysis: The African-American CRASH (AA CRASH) study is an NIH-funded, multicentre, prospective study that enrols African-Americans (n=900) who present to the emergency department (ED) within 24 hours of MVC. Participants are enrolled at 13 ED sites in the USA. Individuals who are admitted to the hospital or who report a fracture or tissue injury are excluded. Participants complete a detailed ED interview that includes an assessment of crash history, current post-traumatic symptoms and health status prior to the MVC. Blood samples are also collected in the ED using PAXgene DNA and PAXgene RNA tubes. Serial mixed-mode assessments 6 weeks, 6 months and 1 year after MVC include an assessment of adverse sequelae, general health status and health service utilisation. The results from this study will provide insights into the incidence and pathogenesis of persistent pain and other post-traumatic sequelae in African-Americans experiencing MVC.

Ethics and dissemination: AA CRASH has ethics approval in the USA, and the results will be published in a peer-reviewed journal.

Strengths and limitations of this study

- African-American CRASH enrols African-Americans, an understudied but highly burdened population, and will determine incidence and risk factors of adverse post-traumatic sequelae following motor vehicle collision trauma in this population.
- Biological samples including blood tubes will be collected and analysed for pathogenic mediators of adverse post-traumatic sequelae.
- Collecting data from 900 participants across 13 emergency departments and at multiple time points has inherent challenges, including potential loss to follow-up and participant heterogeneity.

BACKGROUND

More than 50 million motor vehicle collisions (MVC) occur worldwide each year,[1] and more than 10 million of these MVCs occur each year in the USA.[2] More than 4 million of these individuals present to US emergency departments (EDs) after the MVC for evaluation,[2] and the overwhelming majority (>90%) of these individuals are discharged to home without fracture or other

identifiable injury.[3] Although most of these discharged individuals recover, a substantial proportion develops persistent musculoskeletal pain and/or persistent psychological sequelae such as post-traumatic stress disorder (PTSD).[4–6] The development of these adverse post-traumatic sequelae after MVC constitutes a common, morbid and costly public health problem in industrialised countries.[7–9] The pathogenesis of adverse sequelae after MVC remains poorly understood.

In the USA, more than 1 million African-Americans present to the ED for care after minor MVC each year,[10] but to date no prospective studies of chronic musculoskeletal pain development in African-Americans experiencing MVC have been performed. A study evaluating the incidence and pathogenesis of persistent musculoskeletal pain and other adverse post-traumatic sequelae in African-Americans experiencing MVC is valuable for several reasons. First, African-Americans experience an increased burden of MVCs compared to European Americans.[10] Second, several lines of evidence suggest that African-Americans experience a greater burden of chronic pain development after MVC. For example, in other clinical conditions, African-Americans have been consistently shown to experience a greater burden of chronic pain than European Americans,[11–20] and in laboratory settings, African-Americans have been found to have increased sensitivity to experimental pain.[20–26] Some of this increased vulnerability is likely due to greater socioeconomic disadvantage;[27–29] however, data from other settings demonstrate that worse health outcomes in African-Americans are not accounted for by socioeconomic differences alone.[27 30–32] Third, studies of African-Americans can most effectively evaluate the influence of factors that may be particularly relevant within this ethnic group, such as discrimination. Unfortunately, discrimination is a fundamental aspect of the social structure of the USA and a daily reality for African-Americans.[33–36] Discrimination has been associated with worse mental health outcomes[37] (eg, depression[38–43]) and worse physical health outcomes,[37 44 45] and may influence chronic pain and neuropsychological outcomes after MVC. Finally and more generally, evaluating the pathogenesis of a disorder among a high-risk population using molecular and epidemiological methods is a valuable approach to gaining new insights into disease pathogenesis.[46–49] In this article, we describe the methods of a large-scale, NIH-funded, longitudinal study evaluating the incidence and pathogenesis of chronic pain and neuropsychological outcomes among African-Americans experiencing MVC.

METHODS/DESIGN

Study sites

The African-American (AA) CRASH study is a prospective, multicentre, observational cohort study of African-Americans who have experienced MVC. Study participants are enrolled at research network ED sites and complete an initial interview assessment in the ED. Mixed-mode study participant follow-up assessments are performed at 6 weeks, 6 months and 1 year via phone, web or mail. The study research network ('TRYUMPH Research Network') includes UAB Hospital (Birmingham, Alabama, USA), UF Health Jacksonville (Jacksonville, Florida, USA), Henry Ford Hospital (Detroit, Michigan, USA), Sinai-Grace Hospital (Detroit, Michigan, USA), Albert Einstein Medical Center (Philadelphia, Pennsylvania, USA), Detroit Receiving Hospital (Detroit, Michigan, USA), St. Joseph Mercy Ann Arbor Hospital (Ypsilanti, Michigan, USA), Medstar Washington Hospital Center (Washington DC, USA), Boston Medical Center (Boston, Massachusetts, USA), St. Joseph's Regional Medical Center (Paterson, New Jersey, USA), Spectrum Health Butterworth Hospital (Grand Rapids, Michigan, USA), William Beaumont Hospital (Royal Oak, Michigan, USA) and Baystate Medical Center (Springfield, Massachusetts, USA). The study was approved by the institutional review boards of all participating hospitals. The data coordinating centre for the study is located at the University of North Carolina, Chapel Hill, North Carolina, USA, and the study's IRB approval number is 11-1742.

Inclusion criteria

Patients aged 18–65 years who present to the ED within 24 hours after MVC and who are unlikely to be admitted to the hospital are screened for eligibility. Patients with injuries likely to require hospitalisation are excluded, as are patients with fractures (other than small bone fractures), major lacerations (lacerations more than 20 cm in length or more than 4 lacerations requiring sutures), intracranial injury or spinal injury (defined as vertebral fracture or dislocation, or new neurologic deficit). Patients admitted to the hospital overnight are also excluded, as are prisoners, pregnant patients, patients not alert and oriented, patients whose phone was disconnected in the past year and patients unable to read and understand English. Individuals who are certain at the time of ED presentation that they will litigate are also excluded, to help ensure that a proportion of individuals not engaged in litigation are enrolled. Patients are also excluded if they take opioids above a dose of 20 mg of oxycodone daily or equivalent. In addition, since the goal of the study is to evaluate an African-American sample, only non-Hispanic African-American patients, based on self-report, are evaluated for eligibility. After assessment for eligibility, the patient's consent to participate is obtained in writing and filed in a confidential research file. Enrolment in this ongoing study started in September 2012 and will conclude in September 2016.

Patient screening and consent

Patient screening is performed using a web-based form. Research staff complete this form for each patient presenting to the ED for evaluation during site research

staff screening hours (generally 12–16 hours each day). The web-based screening form prompts the research assistant (RA) to complete a series of questions. If participants are eligible for participation based on these screening questionnaire responses, then the RA is automatically advanced to the ED assessment interview, and individuals are approached for study participation. If individuals are not eligible, the reason for ineligibility is stored by the system. Signed informed consent is obtained from all participants.

ED assessment

The ED setting represents a unique opportunity to collect detailed information from patients shortly after MVC. The proposed research protocol takes substantially less time than patients usually spend waiting in the ED and can generally be completed within this time without prolonging a patient's ED stay. ED assessments are conducted by trained RAs using a standardised web-based questionnaire on laptop computer. Back-up paper copies are used by RAs if hospital wireless internet service is unavailable. The ED interview begins with the collection of patient contact information, including information on two potential alternative contacts. Subsequent interview assessments include the collection of detailed information regarding the collision event, current and past somatic and psychological symptoms, expectations of recovery, general health and medication use (table 1). Participants are compensated $75 for completing the ED evaluation.

Table 1 Study question domains, specific measures and times of assessment

Domain	Measure	ED	6WK	6M	1YR
MVC injury events	Standardised Questionnaire	•			
Distress in response to MVC	Peritraumatic Distress Inventory[50]	•			
Expectations for recovery	Emotional and physical recovery	•			
Dissociative symptoms in response to MVC	Michigan Critical Events Perception Scale[51]	•			
Catastrophizing	Pain Catastrophizing Scale[52]	•			
Fault and Anger	Fault and anger questions relating to MVC	•			
Pre-MVC pain and somatic symptoms	Numeric Pain Rating Scale,[53] Regional Pain Scale,[54] Overall Pain,[55] Somatic Symptom Interview[56]	•			
Pre-MVC general health	Short Form-12[57]	•			
Pre-MVC anxiety symptoms	State-Trait Anxiety Inventory (Form Y)[58]	•			
Pre-MVC depressive symptoms	Center for Epidemiological Studies Depression Scale[59]	•			
Pre-MVC perceived social support	Multidimensional Scale of Perceived Social Support[60]	•			
Pre-MVC depression anxiety	Depression and Anxiety Stress Scale[61]	•			
Experiences of discrimination	Major Experience of Discrimination[62]	•			
Ethnic identity	Multidimensional Inventory of Black Identity[63]	•			
Demographic information	Standard items	•		•	•
Alcohol and drug use	TWEAK,[64] Substance Abuse Outcomes Module[65]	•		•	•
Pre-MVC lifetime trauma exposure	Traumatic Life Events Questionnaire[66]		•		
Current pain symptoms (neck and other pains)	Numeric pain Rating Scale,[53] Regional Pain Scale,[54] Overall Pain,[55] Somatic Symptom Interview[56]	•	•	•	•
Neuropathic pain	DN4[67]	•	•	•	•
Current whiplash	Quebec Classification[68]	•	•	•	•
Fear avoidance	Tampa Scale for Kinesiophobia,[69] Fear Avoidance Beliefs Questionnaire[70]	•	•	•	•
Medication use	Standard items	•	•	•	•
Discrimination	Day to day unfair treatment, Everyday discrimination[62]	•	•	•	•
Disability/litigation claims	Standard items	•	•	•	•
Post-MVC depressive and anxious symptoms	Center for Epidemiological Studies Depression Scale,[59] Depression and Anxiety Stress Scale[61]		•	•	•
PTSD symptoms	Impact of Event Scale-Revised[71]		•	•	•
General health	Short Form-12[57]		•	•	•
New injury or re-injury	Standard items		•	•	•
Pain interference	Brief Pain Inventory (pain interference questions)[72]		•	•	•
Travel anxiety	Travel anxiety questions		•	•	•
Missed work or activities	Standard items		•	•	•
Health service utilisation	Standard items		•	•	•

1YR, 1 year; 6M, 6 months; 6WK, 6 weeks; DN4, neuropathic pain diagnostic questionnaire; ED, emergency department; MVC, motor vehicle collision; PTSD, post-traumatic stress disorder; TWEAK, alcohol screening instrument for pregnant women.

ED blood collection

Blood for DNA is collected using a PAXgene DNA storage tube (8.5 cc). A barcode label is placed on the tube with a sample number, and a handheld barcode reader is used to record the sample in the web-based tracking system and to create a link with the participant's study ID number. (The barcode reader is used to prevent human data entry error.) Each blood sample number is different from the participant's study ID number, to increase confidentiality. DNA blood samples are then refrigerated at the study site and shipped in batches every 2 weeks to the UNC Biospecimen Processing Facility in Chapel Hill, North Carolina, USA. The barcode is also scanned at the time of shipment from the study site to the Biospecimen Processing Facility and at the time of receipt by the Biospecimen Processing Facility so that blood sample chain of custody procedures are maintained and sample location can be continuously monitored.

Blood for RNA are collected using a PAXgene RNA storage tube (2.5 cc). As with the PAXgene DNA tubes, PAXgene RNA storage tubes are labelled with a barcode sample number, which is linked to the participant's study ID number using the barcode reader described above. RNA tubes are frozen immediately at −70°C and shipped in batches 2–3 times a year to the UNC Biospecimen Processing Facility. After follow-up information is collected, personally identifying information is stripped from the database so that banked biological data are de-identified.

Data extraction

Following the participant's ED visit, RAs at each site complete a web-based participant data extraction form. This form collects information from the ED and hospital medical records related to the study participant's care, including the following: ED arrival date and time, participant chief symptom, results of any radiologic evaluations, participant injuries by body region (eg, abrasion, contusion), discharge diagnoses, medications received in the ED and/or prescribed at discharge, patient medical history, drug and alcohol screening and ethnicity of providers. Patient injuries are scored using the Abbreviated Injury Score (AIS) and Injury Severity Score (ISS), and the nature of injury (ICD-9-CM codes) and mechanism of injury (ICD-9 E codes) are recorded. Medical record data are accessed during the course of the study to update patient contact information.

Participant follow-up evaluations at 6 weeks, 6 months and 12 months

At each follow-up evaluation time point, participants have the choice of completing follow-up evaluations online, by telephonic interview or by completing paper versions of the questionnaires and mailing them back to the study team. Questions are worded so that they can be completed by any of the above methods. Paper versions of questionnaires are mailed to all participants at the beginning of the follow-up window so that those who wish to complete the survey via telephonic interview can more easily understand questions and response options. Individuals who instead wish to complete these paper forms and mail them in may do so. Participants are compensated $50, $55 and $65 for completing the 6-week, 6-month and 1-year interviews, respectively.

Follow-up assessments include an evaluation of adverse post-traumatic sequelae such as pain, somatic, depressive, anger and anxiety symptoms as well as medication use, pain interference, fear of movement, experiences of discrimination and general health (table 1). Evaluation of anxiety symptoms at each time point includes an assessment of PTSD symptoms and travel anxiety. Missed work, new or re-injury events and litigation or disability claims are assessed at each follow-up time point. Demographic information and alcohol, tobacco and drug use are assessed at the 6- and 12 month time points.

Study hypotheses and primary and secondary analyses

Primary study hypotheses will evaluate whether (1) the original fear-avoidance model (FAM) of chronic pain development proposed by Vlaeyen and Linton[73] provides a good fit to the data regarding the pathogenesis of chronic axial pain after MVC in African-Americans, (2) past experiences of discrimination influence vulnerability to chronic pain after MVC in African-Americans, (3) ethnic identify modifies any influence by discrimination and (4) genetic variations in key enzymes and transporter molecules affecting neuro/stress/immune system function influence the development of chronic pain after MVC in African-Americans. In addition to the above analyses, the rich bounty of data from this first-ever study of chronic pain development in an African-American sample will be available for many other analyses, including analyses evaluating hypotheses regarding genetic, molecular and epidemiologic factors influencing chronic pain and other adverse post-MVC sequelae and analyses evaluating healthcare utilisation and treatment responses.

Power calculation and proposed statistical analyses

A sister cohort evaluating similar outcomes in European American individuals following MVC was recently completed.[74] As with that study, the present study was powered based on proposed genetic analyses, which require the largest sample size. The previous study, with n=948, had sufficient power to discover genetic variants in a number of genes that predicted adverse post-MVC pain outcomes, including *COMT, OPRM1, FKBP5, DRD2* and *CRHBP*.[75–79] As described above, available data indicate that rates of chronic pain development among African-Americans vs European Americans experiencing traumatic events such as MVC are substantially increased. Thus, we anticipate an equal or greater number of cases in our African-American versus European American cohort, and sufficient power to

address our specific aims. Statistical methods used to evaluate primary and secondary study aims will include structural equation modelling, latent growth curve modelling, multivariate regression modelling and various bioinformatics methods specific to the biological methods employed.[76 78 79]

DISCUSSION

As noted above, to date no prospective studies of chronic pain pathogenesis have been performed in an African-American population, despite evidence that African-Americans experience an increased burden of adverse post-traumatic sequelae such as chronic post-MVC pain.[80] The overarching goal of the present study is to develop tools that identify individuals at high risk of adverse sequelae at the time of ED evaluation, and to develop a better understanding of risk factors and mediators of chronic pain and neuropsychological sequelae after MVC so that effective secondary preventive interventions can be developed.

One aim of the study is to test a well-known cognitive–behavioural FAM of chronic pain development after MVC.[73] Indirect evidence from cross-sectional and experimental studies supports the FAM;[81–83] however, the FAM has been assessed only minimally in prospective cohorts. This study will test the multivariate predictive relationships in the FAM model in a large prospective cohort of individuals at increased risk of chronic pain development.

This cohort study is the sister study to a previously completed study evaluating adverse post-traumatic sequelae, including pain outcomes, in a large cohort of European Americans (n=948) experiencing MVC.[74] Both studies evaluate individuals following the same trauma/stress exposure (MVC), and use very similar methods and a very similar battery of assessments to evaluate individuals across the same follow-up time points (6 weeks, 6 months and 1 year). In the sister cohort study, we had a follow-up rate of ≥90% at each of the three time points. In other studies, follow-up rates for African-Americans are generally lower than for European Americans, due to a greater degree of socioeconomic disadvantage in the population. Therefore, we estimate final loss to follow-up of ~10–15% at each time point in the African-American sample.

Several limitations should be noted when interpreting the results of this study. The first limitation is that we are using self-report to identify African-American individuals, which could result in a heterogeneous population. However, this method of identification is highly valuable because ethnic identity is not only a biological variable but also a multidimensional construct encompassing an individual's attitudes towards group membership. Second, the study is limited to patients who come to the ED after MVC and are discharged to home after evaluation. However, available data indicate that this population constitutes more than 90% of MVC patients who present to the ED for evaluation after MVC.[3] Finally, another limitation is that only about half of the potentially eligible participants are enrolled (based on pilot data analyses). The generalisability of the results among individuals who declined enrolment is not known. However, these limitations are consistent with other studies enrolling participants after an acute aftermath of trauma in an ethical manner.

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Contributors SAM developed the study concept and design. AYL, HEW, PLH, EZ, CL, M-AV, KD, CP, RD, SK, JF, MR, JJ, RS and NR contributed to the acquisition of data, and SAM and ACS supervised the study. KAB provided statistical expertise and assisted in study design. SDL, JH and SAM drafted the manuscript, and all authors made critical revisions of the manuscript for important intellectual content. SDL and SAM take responsibility for the paper as a whole. All authors read and approved the final manuscript.

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Competing interests None declared.

Ethics approval Institutional Review Board (IRB) approved this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement We welcome collaboration and use of these data. To achieve this goal, we will develop a mechanism for data sharing that is consist in HIPAA guidelines and the Final NIH Statement on Sharing Research Data. We will make available coded data (phenotype and genotype) to the

scientific community, and we will work with NIH programme staff to coordinate the development of a coded web-based database that can be accessed by password. Access to these databases will require a formal correspondence requesting access. This request will be reviewed and approved by the programme's investigative team and NIH programme staff prior to granting access to the requested materials.

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