PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Methodology of AA CRASH: A Prospective Observational Study Evaluating the Incidence and Pathogenesis of Adverse Posttraumatic Sequelae in African Americans Experiencing Motor Vehicle Collision
AUTHORS	Linnstaedt, Sarah; Hu, JunMei; Liu, Andrea; Soward, April; Bollen, Kenneth; Wang, Henry; Hendry, Phyllis; Zimny, Erin; Lewandowski, Christopher; Velilla, Marc-Anthony; Damiron, Kathia; Pearson, Claire; Domeier, Robert; Kaushik, Sangeeta; Feldman, James; Rosenberg, Mark; Jones, Jeffrey; Swor, Robert; Rathlev, Niels; McLean, Samuel

VERSION 1 - REVIEW

REVIEWER	Björn Gerdle Linköping University, Linköping, Sweden.
REVIEW RETURNED	02-May-2016

GENERAL COMMENTS	Background: The reader gets the impression that pain is a part of APNS. Pain can hardly be characterized as a neuopsychological item: it is more complicated than that. Method/Design: * "... and who are unlikely to be admitted are screened for eligibility". This is difficult to understand. Please clairify. Patient screening and consent: RA - please explain first mentioned. It is very unclear why blood is collected! It is not mentioned in the introduction. How are these samples related to the aim of the study (i.e. evaluating the incidence and pathogenesis). The manuscript lacks information about primary and secondary outcomes. Table I is not enough in my opinion. The substances and variables obtained from the blood samples are not mentioned in Table I. . The authors must also describe the planned statistical analyses. Even though this is a protocol the authors must more clearly mention limitations in the discussion.

REVIEWER	Sandar Tin Tin University of Auckland, New Zealand
REVIEW RETURNED	19-May-2016

GENERAL COMMENTS	This paper presents the methodology of a multi-center, prospective

	cohort study aiming to investigate chronic pain and psychological sequelae after motor vehicle collision in African Americans. Generally, the study is thoughtfully designed and the manuscript is well written but lacks methodological details. I offer the following suggestions for improvement. • As the study is restricted to Non-Hispanic African American patients, detailed information on how race and ethnicity is measured should be provided. Is it self-reported? What about the mixed-raced group? Will they be included or excluded? • In the methods section, the study's specific objectives and underlying hypotheses should be mentioned; the study's main exposures and outcomes should be specified; and detailed analysis plan should be provided. • What is the estimated drop-out rate? • In the discussion section, the study's limitations should be acknowledged.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Bjorn Gerdle, Linkoping University, Linkoping, Sweden
1. The reader gets the impression that pain is a part of APNS. Pain can hardly be characterized as a neuropsychological item: it is more complicated than that.
Thank you for this suggestion. We have now changed the term to "adverse posttraumatic sequelae" in the manuscript and the title.

2. "... and who are unlikely to be admitted are screened for eligibility". This is difficult to understand. Please clairify. Patient screening and consent: RA - please explain first mentioned.
Thank you for this suggestion.

We have now added the words 'to the hospital' to make the first sentence more clear:
Patients ages 18 to 65 who present to the ED within 24 hours after MVC and who are unlikely to be admitted to the hospital are screened for eligibility.

We also now define the term "RA" as "research assistant" at first use:

The web-based screening form prompts the research assistant (RA) to complete a series of questions.

3. It is very unclear why blood is collected! It is not mentioned in the introduction. How are these samples related to the aim of the study (i.e. evaluating the incidence and pathogenesis)
That you for this suggestion. We have now changed the text in the introductory section to state that we collected blood samples so that we could use molecular methods to study the pathogenesis of adverse sequelae following 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"

4. The manuscript lacks information about primary and secondary outcomes. Table I is not enough in my opinion. The substances and variables obtained from the blood samples are not mentioned in Table 1.
Thank you for this suggestion. We have added the following information to the manuscript:
Primary study hypotheses will evaluate whether (1) the original fear-avoidance model (FAM) of chronic pain development proposed by Vlaeyen and Linton[50] provide 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, and (3) ethnic identify modifies any influence by discrimination; and (4) 3) 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 health care utilization and treatment responses.

5. The authors must also describe the planned statistical analyses.
We have added the following information to the manuscript in a section titled, “Power calculation and proposed statistical analyses”:
A sister cohort evaluating similar outcomes in European American individuals following MVC was recently completed [51]. 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 powered to discover genetic variants in a number of genes that predicted adverse post-MVC pain outcomes, including COMT, OPRM1, FKBP5, DRD2, and CRHBP [52-56]. 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 modeling, latent growth curve modeling, multivariate regression modeling, and various bioinformatics methods specific to the biologic methods employed (e.g. [53, 57, 58]).

6. Even though this is a protocol the authors must more clearly mention limitations in the discussion.
Thank you for bringing this to our attention. We have added a limitations section to the Discussion section:
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 generalizability of the results among individuals who declined enrollment is not known. However, these limitations are consistent with other studies enrolling subjects after an acute aftermath of trauma in an ethical manner. 24,36,38

Reviewer #2: Sandar Tin Tin, University of Auckland, New Zealand
1. As the study is restricted to Non-Hispanic African American patients, detailed information on how race and ethnicity is measured should be provided. Is it self-reported? What about the mixed-raced group? Will they be included or excluded?
Thank you for bringing up this important point. Non-hispanic African Americans were identified in this study based on self-report; we have now added this information in the Methods/Design section of the manuscript and commented on this point in the discussion.

2. In the methods section, the study’s specific objectives and underlying hypotheses should be mentioned; the study’s main exposures and outcomes should be specified; and detailed analysis plan should be provided.

Thank you for this valuable point. We have now added this information as described above.

3. What is the estimated drop-out rate?
Thank you for this question: this information has been added to the Discussion section of the manuscript.
This cohort study is the sister study to a previously completed study evaluating adverse posttraumatic sequelae, including pain outcomes, in a large cohort of European Americans (n = 948) experiencing MVC [51]. 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 timepoints (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 timepoints. 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 approximately 10-15% at each timepoint in the African American sample.

4. In the discussion section, the study's limitations should be acknowledged.
Thank you for bringing this lack of information to our attention. As discussed above, we have added a limitations section to the Discussion of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Björn Gerdle Pain and Rehabilitation Centre, and Department of Medical and Health Sciences, Linköping University, SE 581 85 Linköping, Sweden.
REVIEW RETURNED	26-Jul-2016

GENERAL COMMENTS	I have no further comments. The authors have considered my comments and revised the manuscript well.

REVIEWER	Sandar Tin Tin University of Auckland, New Zealand
REVIEW RETURNED	29-Jul-2016

GENERAL COMMENTS	The authors have addressed the issues raised by the reviewers. The manuscript is now acceptable for publication.