HEALTH PSYCHOLOGY BULLETIN

EDITORIAL HISTORY

The Impact of Cardiac-induced Post-traumatic Stress Disorder Symptoms on Cardiovascular Outcomes: Design and Rationale of the Prospective Observational Reactions to Acute Care and Hospitalizations (ReACH) Study

Jeffrey Birk, Ian Kronish, Bernard Chang, Talea Cornelius, Marwah Abdalla, Joseph Schwartz, Joan Duer-Hefe, Alexandra Sullivan & Donald Edmondson

This document contains the editorial history, organized into three sections. This first section, section 0, provides background information about the paper and the review procedure. Section 1 is organized chronologically and contains the editorial communication and peer review history. Section 2 contains the successive preprints and is organized anti-chronologically.

DOI of article:	10.5334/hpb.16
DOI of this editorial history:	10.5334/hpb.16.pr1
Article submitted:	2018-05-06
Revision submitted:	2018-09-23
Article accepted:	2018-11-16
Executive editor:	Lisa Warner
Senior editor:	Ralf Schwarzer
Peer reviewer A:	Evangelos Karademas
Peer reviewer B:	Walter Bierbauer

Cite this document as:

Birk, J., Kronish, I., Chang, B., Cornelius, T., Abdalla, M., Schwartz, J., Duer-Hefe, J., Sullivan, A., & Edmondson, D. (authors); Karademas, E. & Bierbauer, W. (reviewers); Warner, L. & Schwarzer, R. (editors) (2019) Editorial history for 'The Impact of Cardiac-induced Post-traumatic Stress Disorder Symptoms on Cardiovascular Outcomes: Design and Rationale of the Prospective Observational Reactions to Acute Care and Hospitalizations (ReACH) Study'. *Health Psychology Bulletin*, 3(1). DOI: [http://doi.org/10.5334/hpb.16.pr1](https://doi.org/10.5334/hpb.16.pr1)

Paper abstract

Aims: As many as 1 in 8 acute coronary syndrome (ACS) patients develop posttraumatic stress disorder (PTSD) due to the ACS, and ACS-induced PTSD may increase secondary cardiovascular disease (CVD) risk. However, prior studies have been small and underpowered to test plausible behavioral or biological mechanisms of the hypothesized PTSD–secondary CVD risk association. In this paper, we describe the design and methods of a large prospective observational cohort study to estimate the prognostic significance of ACS-induced PTSD, mechanisms for its association with CVD risk, and emergency department (ED) factors that may increase PTSD risk, in a cohort of patients evaluated for acute coronary syndrome (ACS) in the ED of a large, urban academic medical center.

Methods: The Reactions to Acute Care and Hospitalization (ReACH) study follows 1,741 racially, ethnically, and socioeconomically diverse patients initially presenting to the ED with ACS symptoms. Psychosocial factors are assessed at baseline. Medication adherence is monitored by electronic pill bottle (eCAP). Participants are contacted by phone at 1-, 6-, and 12-months post-hospitalization to assess PTSD symptoms, hospital readmission, and recurrent CVD events/mortality (proactively searched and confirmed by medical records).

Conclusion: This study will provide the most accurate estimates to date of PTSD's association with recurrent CVD events and mortality and will test whether medication adherence mediates that association. Further, it will provide estimates of the contribution of ED and hospital factors to PTSD risk in ACS patients. If our hypotheses are supported, we will have identified PTSD as a novel target for secondary risk reduction.

Background

This peer review history is published under Health Psychology Bulletin's peer review policy. Peer review at Health Psychology Bulletin (HPB) is blind, but upon acceptance of an article, the entire peer review history is made public. This policy has two aims. First, it makes the reviews citable, rewarding reviewers for their reviews, incentivizing thorough, thoughtful reviews, and stimulating constructive, considerate reviews and responses. Second, to yield the best of both worlds in terms of design of the review procedure. The common procedure of shielding authors' and peer reviewers' identities aims to prevent undue harshness or leniency. However, this anonymity also protects reviewers who make unreasonable requests or statements that are inconsistent with the literature, and authors who refuse to respond adequately to reviewers' requests. These risks are ameliorated by unblinding and publishing the peer review procedure upon paper acceptance.

Health Psychology Bulletin

Health Psychology Bulletin (HPB) is an official journal of the European Health Psychology Society (EHPS). It implements a number of innovative practices such as this peer review procedure, a strong full disclosure policy, a two-tiered review procedure, and explicitly welcoming null findings, replications, and reports of lessons learned such as failed manipulations or measurement instruments, as well as regular articles.

Section 1: editorial correspondence

This section is comprised of the editor-author correspondence followed by the review reports in chronological order.

May 6, 2018

Gerjo Kok, Ph.D. and Gjalte-Jorn Peters, Ph.D.
Editors in Chief, Health Psychology Bulletin

Dear Drs. Kok and Peters:

Enclosed please find a manuscript entitled "The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (ReACH) study." We would be grateful if you would consider it for publication in Health Psychology Bulletin.

This manuscript presents the design of a large prospective observational cohort study to test the association between post-traumatic stress disorder (PTSD) induced by acute coronary syndrome (ACS) and secondary cardiovascular (CVD) risk and mortality. The study tests mechanisms for these associations, including diminished adherence to medications, as well as emergency department (ED) factors that may increase PTSD risk. We believe that this study will provide definitive evidence about whether PTSD should be considered as a novel target to be leveraged to reduce CVD risk.

This manuscript is original, not previously published, and not under concurrent consideration elsewhere. Please contact me at the email address, phone number, or mailing address listed below.

Sincerely,

Donald Edmondson, Ph.D., MPH
Associate Professor of Behavioral Medicine
Center for Behavioral Cardiovascular Health
Columbia University Medical Center
Director of Emergency Medicine Research
New York Presbyterian Hospital

Editor/Author Correspondence

Section Editor
2018-08-08 12:34 PM

Subject: [HPB] Editor Decision - "The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (ReACH) study"

Dear Dr Birk,

After review, we have reached a decision regarding your submission to Health Psychology Bulletin, "The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (ReACH) study". Our decision is to request revisions of the manuscript prior to acceptance for publication.

The full review information should be included at the bottom of this email. A summary of the requested edits from the editorial team can be found below. Please consider these points and revise the file accordingly:

Editorial Revision Requests:

Major

- Please download the SPIRIT checklist and comment in each line, whether the information requested is presented in the protocol: www.spirit-statement.org/publications-downloads

- Figure 2 might serve as a substitute for a SPIRIT time table – please check whether all info needed for a SPIRIT time table is provided in Figure 2

- Has the trial been registered prospectively? If yes, please provide the registration number, if not, please register retrospectively and explain this fact in the methods section

- Analyses plan for aims 1 and 2 are well described, please provide similarly detailed plans for aims 3 and 4

Minor

- Interviews in the ED environment might bias the study results as they could possibly serve as intervention: patients, who are being left to wait in the ED usually feel ignored and alone, but patient who take part in this study, will receive at least minimal amounts of attention. This attention is "only" granted by a research assistant, but might nevertheless serve as unspecific social support and reduce the perception of being left alone with symptoms. These possible biasing effects should be account for in the discussion.

- Please check the order of punctuation and references in brackets at some points in the measurement section

- Please assign each measurement point in time with an abbreviation like T1 etc., so they are easier to refer to

- As this is just the protocol it would be ok to leave out the descriptive information on patients recruited so far (but if you would like to include it, that would be ok as well)

- Please provide dois for all references

Highlighting reviewers' comments

- Apart from the fact that all comments made by the reviewers should be responded to in detail, I would like to highlight two of their comments as being of particular importance:

- 1) both feel that the measures could be described in more detail and with information on their validity from previous studies

- 2) Reviewer 2's comment on the logical order of variables assessed at different time points in the mediation analysis also seem highly relevant.

To access your submission account, follow the below instructions:

- 1) login to the journal webpage with username and password

- 2) click on the submission title

- 3) click 'Review' menu option

- 4) download Reviewed file and make revisions based on review feedback

- 5) upload the edited file

- 6) Click the 'notify editor' icon and email the confirmation of re-submission and any relevant comments to the journal.

Please ensure that your revised files adhere to our author guidelines, and that the files are fully copyedited/proofed prior to upload. Please also ensure that all copyright permissions have been attained. This is the last opportunity for major editing, therefore please fully check your file prior to re-submission.

If you have any questions or difficulties during this process, please do contact us.

Please could you have the revisions submitted by [GIVE 2 WEEK DEADLINE]. If you cannot make this deadline, please let us know as early as possible.

Kind regards,

Prof Lisa Marie Warner
MSB Medical School Berlin

Reviewer 1:

The aim of this study is four-fold: (a) to estimate the possible impact of ACS-induced PTSD on future cardiac events/mortality, (b) to examine whether medication adherence mediates the impact of PTSD on subsequent cardiac events, (c) to study factors that may increase the risk for the development of PTSD symptoms, as well as (d) to determine whether patients who are admitted to the emergency room but not finally diagnosed with ACS are similarly at increased risk of PTSD. The manuscript describes a very interesting prospective study with four well-defined and equally important aims, a well-developed methodology that fully covers the study goals, as well as advanced and proper statistical analyses. The manuscript also includes a thorough presentation and discussion of the extant literature on the matter and its limitations. Finally, the manuscript is mostly well-written and clear. Still, there are some points that authors should consider, as the manuscript seems not well-prepared at some points. Specifically,

1. In the Abstract only the first three specific aims of the study are presented. The fourth one, regarding the patients who "rule out" for ACS, is ...forgotten.
2. Also in the Abstract, the aim (c) is vaguely described. The authors refer to "mechanisms for its association..." (line 6). However, the study focuses on only one potential mechanism, namely, medication adherence. Thus, the description of this specific aim in the Abstract could be misleading and should be amended.
3. Page 5, 2nd paragraph – page 6: Without any "warning" (a bit out of the blue), authors begin to describe the fourth aim of the study. This reviewer believes that it would be better to also refer to this fourth aim earlier in the manuscript (as well as in the Abstract), and devote a separate section to this aim.
4. Page 10, 6th line from the bottom: authors refer to the "gold standard screening instrument for PTSD", without any further explanation. This point is quite unclear and should be better explained.
5. It seems that not all measures used in this study are mentioned in the main document. In the Replication Package some more measures/scales are mentioned, while on p. 15, Statistical Approach, line 5, the Patient Health Questionnaire is mentioned for the first time (it was not included in the Measures section of the manuscript). Please, provide a more comprehensive description of the measures used in the study.
6. Finally, I think that another limitation could be mentioned in the relevant section of the Discussion: the focus of the study on a sole possible mechanism (i.e., medication adherence), while there are several more.

Reviewer 2:

This observational study examines the association of acute coronary syndrome (ACS) induced post-traumatic stress disorder (PTSD) and recurrent cardiac events or mortality. 1741 patients were evaluated in emergency department (ED) for ACS (1st point of measurement). The study is comprised of five study phases. The first phase of the study occurred in the ED (interviews and ED characteristics). The second phase occurred after patients were admitted to inpatient care (interview about psychosocial and interpersonal factors). Patients not going to inpatient care completed this second phase by telephone. The third to fifth phases of the study were telephone interviews conducted 1 month, 6 months, and 12 months after enrollment. The 1-month interview assesses PTSD symptoms, cardiac events), as well as extent of and reasons for cardiovascular medication non-adherence. The 6-month and 12-month telephone interviews were largely identical to the 1-month interview. After inpatient care up to the 6-month measurement willing patients tracked their medication intake with an electronic pillbox. The authors propose a theoretical model in which ED factors (e.g. crowding, doctor-patient communication) contribute to the development of PTSD, which in turn could influence the recurrence of cardiac events. A possible mechanism, medication non-adherence is introduced.

Overall, this is a well-written paper. I congratulate the authors for this study, as in my opinion studies with a large number of participants are urgently needed. In addition, the authors present data following up patients up to one year after visiting the emergency department of large hospital in New York (should be blinded).

That being said, I do have several issues that should be addressed before publication seem suitable.

General points:

- a) While reading the manuscript it seemed that some abbreviations were not introduced and described explicitly. This would help readers.
- b) Please provide information regarding ethical approval.
- c) How many participants got the eCAP (electronic bottle)? Do you conclude non-adherence if no opening occurs? Patients might stop using the eCAP but taking the medication.
- d) In section Measures the authors describe a medication non-adherence self-report measurement. As for this review phase results are missing, why did the authors include these measurements in the manuscript? In addition, I would like to challenge the validity of the one item measurement of medication intake. Please interpret these results with caution as, in my opinion, these broad medication intake scales are in part responsible for some low adherence rates published in literature.
- e) Please provide information on the validity of your measures
- f) There are some differential diagnoses to PTSD which should be discussed e.g., adjustment disorder. The symptoms of adjustment disorder don't quite reach the level of PTSD.

Study aim 2: Determine whether electronically-measured medication nonadherence mediates any association of

suspected ACS-induced PTSD with CVD risk:

2a) Testing this mechanism seems highly relevant and I am very much looking forward to the results. However, in a mediation model a certain causal process is highlighted which is not correctly presented by the authors. Page 15 (Statistical approach) the authors introduce the following mediation model: predictor X (PTSD, assessed at 1-month), mediator M (medication adherence, measured before X) and outcome Y (cardiac events, measured 1-month – 12 month). In order to meet the requirements for mediation analysis, in my opinion, the authors should look at medication adherence following the 1-month interview thereby the underlying causal order is not violated. Study aim 3: Identify predictors of suspected ACS-induced PTSD that are related to the patient, the physicians, and the ED environment:

3a) Quality of doctor-patient communication: I am no expert in this field of research, however, it is highly irritating to me to classify discordance in ethnicity and first language as quality of communication. This should be reframed / critically discussed what was actually measured.

3b) Please include a reference for the social support measurement.

Study aim 4: Determine whether patients who “rule out” for ACS are similarly at increased risk of PTSD and adverse CVD outcomes

4a) Do you plan to include these patients to your primary research question (study aim 1 – 3)? I would argue for a sub-group analysis as patients who got ruled out for ACS do not share the same trajectories than patients with ACS.

4b) In general, my enthusiasm regarding study aim 4 is low. Receiving a PTSD diagnosis after getting ruled out for ACS seems bold.

Health Psychology Bulletin
<http://healthpsychologybulletin.com>

Author
2018-09-23 09:30 PM

Subject: The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (ReACH) study

September 23, 2018

Dear Drs. Warner and Schwarzer,

Enclosed please find the revised version of our manuscript entitled “The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (REACH) study.” I would be grateful if you would consider this revised manuscript for publication in Health Psychology Bulletin.

We thank you for your insightful comments, which have strengthened the paper. The manuscript has been substantially revised to describe the measures more fully, to provide psychometric validation information about measures, and to clarify details about the analytical approach. Furthermore, we ensured that we followed the STROBE guidelines for observational cohort trials—see the completed STROBE checklist with this submission, we addressed concerns about the temporal separation and order of variables in the planned mediation analysis, and we corrected various minor points (e.g., added dois to references, added information about ethical approval).

This manuscript is original, not previously published, and not under concurrent consideration elsewhere. Please contact me at the email address, phone number, or mailing address listed below.

Sincerely,

Donald Edmondson, Ph.D., MPH
Associate Professor of Behavioral Medicine
Center for Behavioral Cardiovascular Health
Columbia University Medical Center
Director of Emergency Medicine Research
New York Presbyterian Hospital
622 W 168th Street, PH 9-317
New York, NY 10032
P 212.342.3674
F 212.305.0312
dee2109@columbia.edu

Health Psychology Bulletin
<http://healthpsychologybulletin.com>

Section Editor
2018-11-16 10:12 AM

Subject: [HPB] Editor Decision - "The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (ReACH) study"

Dear Dr Jeffrey L. Birk,

After review, we have reached a decision regarding your submission to Health Psychology Bulletin, "The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (ReACH) study", and are happy to accept your submission for publication, pending the completion of copyediting and formatting processes.

As there are no further reviewer revisions to make, you do not have to complete any tasks at this point. The accepted submission will now undergo final copyediting. You will be contacted once this is complete to answer any queries that may have arisen during copyediting and to allow a final chance to edit the files prior to typesetting. If you wish to view your submission during this time, you can log in via the journal website.

The review information should be included in this email.

Kind regards,

Prof Lisa Marie Warner
MSB Medical School Berlin
lisa.warner@medicalschooll-berlin.de

Health Psychology Bulletin
<http://healthpsychologybulletin.com>

Subject

The Impact of Cardiac-induced Post-traumatic Stress

Add Comment

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Review Form Response

Empirical Paper

This review form consists of two sections. This first section is intended as a tool to quickly inspect the required and optional components of this submission. The second section contains the actual review.

Section 1a, Full Disclosure: Replication Package:

Note that for any of these elements, an explanation by the authors as to why this element is omitted, also serves, that is, if the explanation is acceptable. After all, one of HPB's goals is to help emptying the file drawers, and older studies may no longer have all these resources available.

- ☒ Includes protocols for recruitment of participants and guiding participants through the study
- ☒ Includes templates for communications with participants (if applicable)
- ☒ Includes operationalisations of measurements (e.g. questionnaires, source code)
- ☒ Includes operationalisations of manipulations (e.g. intervention manuals, stimuli, etc)
- ☒ Includes analysis plan
- ☒ Includes proposal for ethical approval
- ☒ Includes confirmation of ethics approval/Institutional Review Board (IRB) approval

If applicable, please indicate here to the authors what exactly was omitted, or which resources were not provided in an open format:

Section 1b, Full Disclosure: Analysis Package:

Note that for any of these elements, an explanation by the authors as to why this element is omitted, also serves, that is, if the explanation is acceptable. After all, one of HPB's goals is to help emptying the file drawers, and older studies may no longer have all these resources available.

- ☐ Includes raw data
- ☐ Includes analysis scripts used to clean/preprocess/wrangle/munge the data
- ☐ Includes cleaned data
- ☒ Includes analysis scripts used to conduct statistical analyses
- ☐ Includes textual output
- ☐ Includes graphical output

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Section 2a, Reviewer comments:

Here, please type or paste your review. Please make sure to adhere to the [editorial policy for reviewers](#).

The aim of this study is four-fold: (a) to estimate the possible impact of ACS-induced PTSD on future cardiac events/mortality, (b) to examine whether medication adherence mediates the impact of PTSD on subsequent cardiac events, (c) to study factors that may increase the risk for the development of PTSD symptoms, as well as (d) to determine whether patients who are admitted to the emergency room but not finally diagnosed with ACS are similarly at increased risk of PTSD. The manuscript describes a very interesting prospective study with four well-defined and equally important aims, a well-developed methodology that fully covers the study goals, as well as advanced and proper statistical analyses. The manuscript also includes a thorough presentation and discussion of the extant literature on the matter and its limitations. Finally, the manuscript is mostly well-written and clear.

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Section 2b, Guidelines and unblinding and publishing of reviews:

Note that this is not a regular reviewing procedure. As you'll see in the [editorial policy for reviewers](#), there should normally be only one reason to reject a paper, and that is if the authors refuse to revise the paper (on the basis of review comments) such that the conclusions are consistent with those that can be drawn based on the data.

In other words, HPB does not reject 'failed' or even 'flawed' research, as long as the failures and flaws are explicitly discussed, and the authors refrain from drawing conclusions not permitted by the data. As a reviewer, therefore, your goal is to scrutinize the paper for transparency and integrity, and help the authors improve their manuscript to achieve that. In addition, the journal has a strong Full Disclosure policy, so where authors do not provide their materials, data, or analysis scripts, they should clearly justify this. We explain the rationale underlying these policies in the [initial editorial](#).

Note also that although the review procedure is double blind, the review history will be made public once a paper has been accepted. The blinding and unblinding is implemented to combine the best of both worlds: blind peer reviews are designed to prevent unreasonably mild or harsh reviews based on author identity, while unblinding upon acceptance prevents the opposite (using the cover of anonymity to be unreasonable) and encourages a civil tone. The review history will also become citable, which is a way of rewarding reviewers for their reviews, but also enables continuing the scientific debate. *

☒ I understand that reviews and editorial communication will be mandatorily unblinded and published upon an accepted article's publication.

Close

* Denotes required field

Review Form Response

Empirical Paper

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If applicable, please indicate here to the authors what exactly was omitted, or which resources were not provided in an open format:

Statement regarding ethical approval is missing.

Section 1b, Full Disclosure: Analysis Package:

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Overall, this is a well-written paper. I congratulate the authors for this study, as in my opinion studies with a large number of participants are urgently needed. In addition, the authors present data following up patients up to one year after visiting the emergency department of large hospital in New York (should be blinded).

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Study aim 2: Determine whether electronically-measured medication nonadherence mediates any association of suspected ACS-induced PTSD with CVD risk:

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Editor

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Comment 2. Editorial Revision Requests: Major: Please download the SPIRIT checklist and comment in each line, whether the information requested is presented in the protocol:

www.spirit-statement.org/publications-downloads

Response 2. Our observational cohort study is not a clinical trial because we do not prospectively assign participants to one or more interventions. Therefore the STROBE checklist for observational cohort studies (Von Elm et al., 2007) is the appropriate one to use instead of the SPIRIT checklist for clinical trials (Chan et al., 2013). We ensured that we addressed each of the relevant items in the checklist, and we have included the completed STROBE checklist as a supplementary document with relevant page numbers associated with each item. The exceptions, of course, are those items pertaining to results and discussion that are not relevant because this is a design and rationale paper rather than a manuscript presenting research findings.

Comment 3. Figure 2 might serve as a substitute for a SPIRIT time table – please check whether all info needed for a SPIRIT time table is provided in Figure 2

Response 3. Following the comment above, we followed the guidelines of the STROBE statement for cohort studies rather than the SPIRIT statement for clinical trials. Related to that point, there is no equivalent of the SPIRIT timetable for STROBE studies. Figure 2 in the paper clearly outlines the timeline of the study. To be sure that the study time points are clear, we have added the following text to the note for Figure 2: “The eligibility screening and informed consent processes occur at the ED in the left-most time point on the timeline. Baseline assessments occur at the in-hospital ED (T1) and inpatient (T2) time points. Outcome variables are measured from the inpatient time point until up to 6 months for medication adherence and at the 1-month (T3), 6-month (T4), and 12-month (T5) time points for the other study outcome measures” (p. 28).

Comment 4. Has the trial been registered prospectively? If yes, please provide the registration number, if not, please register retrospectively and explain this fact in the methods section.

Response 4. The study was not registered on clinicaltrials.gov since it is not a clinical trial (see also our response to the editor’s comment’s 2 and 3 above). We consider this design-and-rationale paper—which includes a publication of the full disclosure package, including replication package, analysis package, informed consent materials, questionnaires, and study information sheets—to be a kind of study registration. In addition, we plan to post the study data in the Open Science Framework (<https://osf.io>).

Comment 5. Analyses plan for aims 1 and 2 are well described, please provide similarly detailed plans for aims 3 and 4.

Response 5. We have added further explanation under the heading “Statistical approach” regarding aims 3 and 4: “Regarding the third aim, multiple regression models will be used to test the associations of patient, physician, and ED factors with subsequent 1-month PTSD symptoms induced by suspected ACS. As an exploratory aim, we will determine whether patients who “rule out” for ACS are at similarly increased risk of PTSD and adverse CVD outcomes in a Cox proportional hazards regression that compares survival functions for patients with confirmed ACS versus those who rule out for ACS at baseline” (pp. 16-17). Additionally, we have provided detailed syntax for addressing aims 3 and 4 in the analysis package with this submission.

Comment 6. Minor: Interviews in the ED environment might bias the study results as they could possibly serve as intervention: patients, who are being left to wait in the ED usually feel ignored and alone, but patient who take part in this study, will receive at least minimal amounts of attention. This attention is “only” granted by a research assistant, but might nevertheless serve as unspecific social support and reduce the perception of being left alone with symptoms. These possible biasing effects should be account for in the discussion.

Response 6. While we agree that it is certainly possible that being questioned by a researcher in the ED may be perceived to some extent as unspecific social support, we nevertheless have observed in previous studies that patients who are approached in the ED do indeed report substantial levels of threat perceptions (with substantial variability as well) and that these symptoms do correlate positively with PTSD symptoms (e.g., Meli et al., 2017). Furthermore, because it is not practically feasible to assess threat perceptions in real time in the ED without at all interacting with patients in the ED, we have not added this point as a study limitation in the manuscript.

Comment 7. Please check the order of punctuation and references in brackets at some points in the measurement section.

Response 7. Thank you. We have fixed these errors.

Comment 8. Please assign each measurement point in time with an abbreviation like T1 etc., so they are easier to refer to.

Response 8. We have added clarification about the five measurement points: Time 1 (T1) at the emergency department, Time 2 (T2) during the inpatient phase, Time 3 (T3) at 1 month after hospital discharge, Time 4 (T4) at 6 months after discharge, and Time 5 (T5) at 12 months after discharge (see p. 10 and pp. 12-15).

Comment 9. As this is just the protocol it would be ok to leave out the descriptive information on patients recruited so far (but if you would like to include it, that would be ok as well).

Response 9. We would prefer to retain the reporting of the descriptive information regarding the recruited study patients in Table 1. We regard the diversity of the sample as a strength of our study.

Comment 10. Please provide dois for all references.

Response 10. We have added the dois to the references.

Comment 11. Highlighting reviewers' comments: Apart from the fact that all comments made by the reviewers should be responded to in detail, I would like to highlight two of their comments as being of particular importance: 1) both feel that the measures could be described in more detail and with information on their validity from previous studies

Response 11. We have added text about the psychometric properties of the self-report measures used in this study. Critically, this newly added information pertains not just to the often used measures of PTSD symptoms, depressive symptoms, and acute stress disorder symptoms, but also to the relatively novel measurement of threat perceptions in the emergency department (ED), a new measure which has been recently shown to have adequate convergent validity and reliability (Cornelius et al., 2018). See the information about validity and reliability of the study measures on pp. 13-14. Please see our responses to Reviewer #1's comment 6 and Reviewer #2's comments 5 and 6 below.

Comment 12. 2) Reviewer 2's comment on the logical order of variables assessed at different time points in the mediation analysis also seem highly relevant.

Response 12. We agree that the temporal order of variables is important for the mediation analysis. We have several reasons for choosing the particular timeframes for each of the measures entered in the mediation analysis. We have given careful consideration to the timing of measurement of the predictor, proposed mediator, and the outcome measure in the mediation analysis. We appreciate the reviewer's concern that the temporal order of the predictor and mediator should be considered. There are three reasons for our analytical plan in which the mediator—medication adherence—is assessed up until the time of the 1-month interview. First, by using this timing for the assessment of the proposed mediator (i.e., prior to 1 month), we ensured that there would be no overlap with the timing of the outcome measure of health outcomes (i.e., after 1 month until 12 months). We determined that it was more important to provide temporal separation between the mediator and the outcome than between the predictor and the mediator, particularly because the reporting of PTSD symptoms is retrospective in that participants are asked to report on the 30-day period leading up to the 1-month assessment.

Second, medication adherence should be relatively stable over time such that assessing it during the first month after hospitalization should be an acceptable approach. Third, it is evident from preliminary data that we are better able to leverage statistical power by including data from a larger number of participants if we include medication adherence data prior to 1 month than if we were to require that the period of measurement be entirely after the 1-month interview. Despite those considerations, we acknowledge that the overlap in time between the predictor and mediator may still be a concern. Therefore, in addition to the main analysis, we will also model adherence over the full eCAP monitoring period (including both pre-1-month and post-1-month) as a sensitivity analysis.

Reviewer #1

Comment 1. The aim of this study is four-fold: (a) to estimate the possible impact of ACS-induced PTSD on future cardiac events/mortality, (b) to examine whether medication adherence mediates the impact of PTSD on subsequent cardiac events, (c) to study factors that may increase the risk for the development of PTSD symptoms, as well as (d) to determine whether patients who are admitted to the emergency room but not finally diagnosed with ACS are similarly at increased risk of PTSD. The manuscript describes a very interesting prospective study with four well-defined and equally important aims, a well-developed methodology that fully covers the study goals, as well as advanced and proper statistical analyses. The manuscript also includes a thorough presentation and discussion of the extant literature on the matter and its limitations. Finally, the manuscript is mostly well-written and clear.

Comment 2. Still, there are some points that authors should consider, as the manuscript seems not well-prepared at some points. Specifically, 1. In the Abstract only the first three specific aims of the study are presented. The fourth one, regarding the patients who “rule out” for ACS, is ...forgotten.

Response 2. The research question regarding patients who rule out for ACS is not highlighted in the abstract because it is an exploratory aim that was not proposed in our grant application for the study. We have edited the manuscript accordingly to reflect that this is not a specific aim of the study but rather an exploratory research question.

Comment 3. 2. Also in the Abstract, the aim (c) is vaguely described. The authors refer to “mechanisms for its association...” (line 6). However, the study focuses on only one potential mechanism, namely, medication adherence. Thus, the description of this specific aim in the Abstract could be misleading and should be amended.

Response 3. It is true that in the present study we highlight medication adherence as just one of several potential mechanisms by which ACS-induced PTSD may influence health outcomes. We have edited the relevant sentence in the abstract to reflect this point: “This study will provide the most accurate estimates to date of PTSD’s association with recurrent CVD events and mortality and will test whether medication adherence mediates that association” (p. 2).

Comment 4. 3. Page 5, 2nd paragraph – page 6: Without any “warning” (a bit out of the blue), authors begin to describe the fourth aim of the study. This reviewer believes that it would be better to also refer to this fourth aim earlier in the manuscript (as well as in the Abstract), and devote a separate section to this aim.

Response 4. As mentioned above in our response to the editor’s comment 2, this aim is exploratory and was not included in the original grant application for this study. We have edited the section about this research question to introduce it properly: “Not all patients who are initially evaluated for ACS in the ED will later be confirmed to have ACS. Therefore our study data provide an opportunity to determine whether patients who “rule out” for ACS are similarly at increased risk of PTSD and adverse CVD outcomes as patients with confirmed ACS. Thus, an exploratory aim of the study is to test whether risk for these adverse outcomes differs according to true ACS vs. ACS rule-out status” (p. 9).

Comment 5. 4. Page 10, 6th line from the bottom: authors refer to the “gold standard screening instrument for PTSD”, without any further explanation. This point is quite unclear and should be better explained.

Response 5. The PCL is a valid and reliable measure for assessing PTSD symptoms in a civilian population. It has specifically been validated with respect to an instrument that is widely considered the true “gold standard” for assessing PTSD: the clinician-administered PTSD scale (CAPS). Therefore we have amended the text as follows: “A third limitation is that PTSD is assessed only by self-reported measures and not by psychiatric interview in this study. However, with respect to the gold standard measure for assessing PTSD, the clinician-administered PTSD scale (CAPS; Blake, 1990), the PCL is a PTSD screening tool that has a valid symptom severity index (Ruggiero, Ben, Scotti, & Rabalais, 2003)” (p. 19).

Comment 6. 5. It seems that not all measures used in this study are mentioned in the main document. In the Replication Package some more measures/scales are mentioned, while on p. 15, Statistical Approach, line 5, the Patient Health Questionnaire is mentioned for the first time (it was not included in the Measures section of the manuscript). Please, provide a more comprehensive description of the measures used in the study.

Response 6. Thank you for noticing this discrepancy. We have added the description of these measures and their citations to the manuscript itself in the Measures section. In particular, the first set of additions now appear under the heading “*Phase I: In the ED (T1)*”: “After consenting patients provide authorization to release medical records, they then provide demographic information and ...” (p. 12). The second set of additions appear under the heading “*Phase 2: Inpatient (T2)*”: “Additionally, the following items and scales are collected at T2: recall of ED threat perceptions (parallel to ED threat perception items administered at T1), the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989), the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1994), the International Physical

Activity Questionnaire (IPAQ; Craig et al., 2003), and the Life Events Checklist (LEC; Gray, Litz, Hsu, & Lombardo, 2004)” (p. 14).

Comment 7. 6. Finally, I think that another limitation could be mentioned in the relevant section of the Discussion: the focus of the study on a sole possible mechanism (i.e., medication adherence), while there are several more.

Response 7. We agree. We have added the following text to the limitations: “Finally, it should be noted that the present study focuses on medication adherence, which is just one of several potential mechanisms by which ACS-induced PTSD may influence health outcomes. Other examples of potential mechanisms include autonomic imbalance, low physical activity, and disrupted sleep (for a review, see Edmondson & von Kanel, 2017).” (p. 19).

Reviewer #2

Comment 1. This observational study examines the association of acute coronary syndrome (ACS) induced post-traumatic stress disorder (PTSD) and recurrent cardiac events or mortality. 1741 patients were evaluated in emergency department (ED) for ACS (1st point of measurement). The study is comprised of five study phases. The first phase of the study occurred in the ED (interviews and ED characteristics). The second phase occurred after patients were admitted to inpatient care (interview about psychosocial and interpersonal factors). Patients not going to inpatient care completed this second phase by telephone. The third to fifth phases of the study were telephone interviews conducted 1 month, 6 months, and 12 months after enrollment. The 1-month interview assesses PTSD symptoms, cardiac events), as well as extent of and reasons for cardiovascular medication non-adherence. The 6-month and 12-month telephone interviews were largely identical to the 1-month interview. After inpatient care up to the 6-month measurement willing patients tracked their medication intake with an electronic pillbox. The authors propose a theoretical model in which ED factors (e.g. crowding, doctor-patient communication) contribute to the development of PTSD, which in turn could influence the recurrence of cardiac events. A possible mechanism, medication non-adherence is introduced. Overall, this is a well-written paper. I congratulate the authors for this study, as in my opinion studies with a large number of participants are urgently needed. In addition, the authors present data following up patients up to one year after visiting the emergency department of large hospital in New York (should be blinded).

Comment 2. That being said, I do have several issues that should be addressed before publication seem suitable. General points: a) While reading the manuscript it seemed that some abbreviations were not introduced and described explicitly. This would help readers.

Response 2. We have edited the manuscript to ensure that abbreviations have been properly introduced in the abstract and in the body of the paper.

Comment 3. b) Please provide information regarding ethical approval.

Response 3. We have added a statement about IRB approval to the manuscript in the Methods section: “After the researchers explain the study and answers any questions that arise, patients who choose to participate provide informed consent. All study protocols have been approved by the Columbia University Medical Center Institutional Review Board” (p. 10).

Comment 4. c) How many participants got the eCAP (electronic bottle)? Do you conclude non-adherence if no opening occurs? Patients might stop using the eCAP but taking the medication.

Response 4. Of the 1,741 participants in the ReACH study covered in this manuscript, 730 participants have been sent the eCAP medication monitoring devices. This number is necessarily considerably lower than the total number of participants in part because the ancillary study began after the main study. We added the following text to the manuscript: “Of those 1,741 participants, 730 participants were sent eCAP devices (see Measures section below) for participation in the ancillary medication adherence study. (This number is necessarily considerably lower than the total number of participants in part because the ancillary study began after the main study)” (p. 11). Regarding the second question, it is possible that participants characterized as nonadherent are adherent to the pills but simply not adherent to the eCAP device. That is an inherent limitation of electronic monitoring. For this reason we plan to conduct a sensitivity analysis excluding participants with 0% medication adherence.

Comment 5. d) In section Measures the authors describe a medication non-adherence self-report measurement. As for this review phase results are missing, why did the authors include these measurements in the manuscript? In addition, I would like to challenge the validity of the one item measurement of medication intake. Please interpret these results with caution as, in my opinion, these broad medication intake scales are in part responsible for some low adherence rates published in literature.

Response 5. Regarding the first question, we opted to include all relevant measures even before study results are available for the sake of completeness in order to represent the full scope of the study. Regarding the second point, we agree about the questionable validity of a single-item measure. This measure of extent of nonadherence is included to supplement the more important objective measure of medication adherence behavior that is assessed unobtrusively by the eCAP devices. There is no gold standard for self-reported medication adherence (Lavsa, Holzworth, & Ansani, 2011), and therefore we opted to include a short, simple, clear measure with high face validity to supplement the eCAP measure.

Comment 6. e) Please provide information on the validity of your measures

Response 6. Please see our response to the editor’s comment 11 above regarding this same question. We made extensive edits to the revised manuscript.

Comment 7. f) There are some differential diagnoses to PTSD which should be discussed e.g., adjustment disorder. The symptoms of adjustment disorder don't quite reach the level of PTSD.

Response 7. We agree that there are differential diagnoses to consider other than PTSD induced by medical events. Whatever the psychological distress is called (PTSD or otherwise), we argue that the literature clearly indicates that these psychological symptoms can be severe for some ACS patients and that they are associated with worsened health behaviors (Kronish, Edmondson, Goldfinger, Fei, & Horowitz, 2012; Monane, Sanchez, Kronish, Edmondson, & Diaz, 2018) and worsened cardiovascular prognosis (Edmondson et al., 2012). We agree with the reviewer that adjustment disorder is not necessarily a poor fit for the elevated symptoms of psychological distress assessed by the PCL. As stated by Sumner and Edmondson (2018), "no matter what we call these PTSD-like symptoms, this psychological response to illness is significant and has consequences for functioning" (p. 86).

Comment 8. Study aim 2: Determine whether electronically-measured medication nonadherence mediates any association of suspected ACS-induced PTSD with CVD risk: 2a) Testing this mechanism seems highly relevant and I am very much looking forward to the results. However, in a mediation model a certain causal process is highlighted which is not correctly presented by the authors. Page 15 (Statistical approach) the authors introduce the following mediation model: predictor X (PTSD, assessed at 1-month), mediator M (medication adherence, measured before X) and outcome Y (cardiac events, measured 1-month – 12 month). In order to meet the requirements for mediation analysis, in my opinion, the authors should look at medication adherence following the 1-month interview thereby the underlying causal order is not violated.

Response 8. As noted above, we have given careful consideration to the timing of measurement of the predictor, proposed mediator, and the outcome measure in the mediation analysis. Please see our full response to this concern in our response to the editor's comment 12 above.

Comment 9. Study aim 3: Identify predictors of suspected ACS-induced PTSD that are related to the patient, the physicians, and the ED environment: 3a) Quality of doctor-patient communication: I am no expert in this field of research, however, it is highly irritating to me to classify discordance in ethnicity and first language as quality of communication. This should be reframed / critically discussed what was actually measured.

Response 9. We have amended the text to avoid characterizing these discordances between doctors and patients as indicative of quality of communication. The new text avoids the word "quality" altogether: "Characteristics of doctor-patient communication during ED evaluation are assessed during the inpatient interview using The Interpersonal Processes of Care Survey (Stewart, Nápoles-Springer, Gregorich, & Santoyo-Olsson, 2007). Patient-doctor discordances in race, ethnicity, and first language are assessed" (p. 13).

Comment 10. 3b) Please include a reference for the social support measurement.

Response 10. The items relevant to social support are described under the heading “*Phase 2: Inpatient (T2)*”: “Social support in the ED is assessed by participant report of who was present with them in the ED, as well as the degree to which the interpersonal support provided to them was appropriate for the event, whether the patient chose to receive the support, and the quality of the participant’s relationship with the support provider” (p. 13). These items are not part of a larger scale but rather are individual questions written specifically to capture our patients’ experiences of support from the family and/or friends who accompany them to the ED. Therefore there is no citation to provide for those particular items.

Comment 11. Study aim 4: Determine whether patients who “rule out” for ACS are similarly at increased risk of PTSD and adverse CVD outcomes: 4a) Do you plan to include these patients to your primary research question (study aim 1 – 3)? I would argue for a sub-group analysis as patients who got ruled out for ACS do not share the same trajectories than patients with ACS.

Response 11. Yes, all patients are included in the three study aims as initially proposed in the grant application for this study. As suggested in this comment, we are planning a sub-group analysis as part of the exploratory aim: “As an exploratory aim, we will determine whether patients who “rule out” for ACS are at similarly increased risk of PTSD and adverse CVD outcomes in a Cox proportional hazards regression that compares survival functions for patients with confirmed ACS versus those who rule out for ACS at baseline” (p. 17). The syntax for this analysis is provided in the attached analysis package.

Comment 12. 4b) In general, my enthusiasm regarding study aim 4 is low. Receiving a PTSD diagnosis after getting ruled out for ACS seems bold.

Response 12. We would like to clarify that our main focus regarding PTSD is not on making a clinical diagnosis of the disorder but rather on assessing the extent of symptoms measured using a validated instrument for measuring PTSD symptoms that is keyed to each patient’s medical event that precipitated the visit to the ED. As we noted in our response to Reviewer #2’s comment 7 above, we recognize that PTSD may not always be the best diagnostic label that accounts for patients’ elevated symptoms of extreme psychological distress following suspected ACS. Critically, we should emphasize that patients with confirmed ACS and rule-out patients are actually much more similar than might be expected with respect to long-term psychological distress resulting from their medical conditions. Specifically, previous research has revealed that ED threat perceptions predicted subsequent PTSD symptoms similarly for a sample of patients evaluated for ACS (confirmed and rule-out) as for the subset of patients with confirmed ACS (Meli et al., 2017).

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Review Form Response

Empirical Paper

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Section 1a, Full Disclosure: Replication Package:

Note that for any of these elements, an explanation by the authors as to why this element is omitted, also serves, that is, if the explanation is acceptable. After all, one of HPB's goals is to help emptying the file drawers, and older studies may no longer have all these resources available.

- ☒ Includes protocols for recruitment of participants and guiding participants through the study
- ☒ Includes templates for communications with participants (if applicable)
- ☒ Includes operationalisations of measurements (e.g. questionnaires, source code)
- ☒ Includes operationalisations of manipulations (e.g. intervention manuals, stimuli, etc)
- ☒ Includes analysis plan
- ☒ Includes proposal for ethical approval
- ☒ Includes confirmation of ethics approval/Institutional Review Board (IRB) approval

If applicable, please indicate here to the authors what exactly was omitted, or which resources were not provided in an open format:

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- ☐ Includes cleaned data
- ☐ Includes analysis scripts used to conduct statistical analyses
- ☐ Includes textual output
- ☐ Includes graphical output

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Section 2a, Reviewer comments:

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Authors have done a great work in addressing reviewers' concerns and the revised document is well improved.

Section 2b, Guidelines and unblinding and publishing of reviews:

Note that this is not a regular reviewing procedure. As you'll see in the [editorial policy for reviewers](#), there should normally be only one reason to reject a paper, and that is if the authors refuse to revise the paper (on the basis of review comments) such that the conclusions are consistent with those that can be drawn based on the data.

In other words, HPB does not reject 'failed' or even 'flawed' research, as long as the failures and flaws are explicitly discussed, and the authors refrain from drawing conclusions not permitted by the data. As a reviewer, therefore, your goal is to scrutinize the paper for transparency and integrity, and help the authors improve their manuscript to achieve that. In addition, the journal has a strong Full Disclosure policy, so where authors do not provide their

materials, data, or analysis scripts, they should clearly justify this. We explain the rationale underlying these policies in the [initial editorial](#).

Note also that although the review procedure is double blind, the review history will be made public once a paper has been accepted. The blinding and unblinding is implemented to combine the best of both worlds: blind peer reviews are designed to prevent unreasonably mild or harsh reviews based on author identity, while unblinding upon acceptance prevents the opposite (using the cover of anonymity to be unreasonable) and encourages a civil tone. The review history will also become citable, which is a way of rewarding reviewers for their reviews, but also enables continuing the scientific debate. *

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Review Form Response

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- ☒ Includes templates for communications with participants (if applicable)
- ☒ Includes operationalisations of measurements (e.g. questionnaires, source code)
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If applicable, please indicate here to the authors what exactly was omitted, or which resources were not provided in an open format:

Section 1b, Full Disclosure: Analysis Package:

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- ☐ Includes raw data
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- ☐ Includes textual output
- ☐ Includes graphical output

If applicable, please indicate here to the authors what exactly was omitted, or which resources were not provided in an open format:

Section 2a, Reviewer comments:

Here, please type or paste your review. Please make sure to adhere to the [editorial policy for reviewers](#).

The authors comprehensively revised their paper along the lines I suggested. I congratulate the authors to their fine piece of work.

Section 2b, Guidelines and unblinding and publishing of reviews:

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Section 2: manuscript iterations

This section is comprised of the manuscript preprints in anti-chronological order (i.e. the originally submitted manuscript is placed last, preceded by the revisions, with the penultimate version directly following this title page).

The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (ReACH) study

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Abstract

Aims: As many as 1 in 8 acute coronary syndrome (ACS) patients develop posttraumatic stress disorder (PTSD) due to the ACS, and ACS-induced PTSD may increase secondary cardiovascular disease (CVD) risk. However, prior studies have been small and underpowered to test plausible behavioral or biological mechanisms of the hypothesized PTSD-secondary CVD risk association. In this paper, we describe the design and methods of a large prospective observational cohort study to estimate the prognostic significance of ACS-induced PTSD, mechanisms for its association with CVD risk, and emergency department (ED) factors that may increase PTSD risk, in a cohort of patients evaluated for acute coronary syndrome (ACS) in the ED of a large, urban academic medical center.

Methods: The Reactions to Acute Care and Hospitalization (ReACH) study follows 1,741 racially, ethnically, and socioeconomically diverse patients initially presenting to the ED with ACS symptoms. Psychosocial factors are assessed at baseline. Medication adherence is monitored by electronic pill bottle (eCAP). Participants are contacted by phone at 1-, 6-, and 12-months post-hospitalization to assess PTSD symptoms, hospital readmission, and recurrent CVD events/mortality (proactively searched and confirmed by medical records).

Conclusion: This study will provide the most accurate estimates to date of PTSD's association with recurrent CVD events and mortality and will test whether medication adherence mediates that association. Further, it will provide estimates of the contribution of ED and hospital factors to PTSD risk in ACS patients. If our hypotheses are supported, we will have identified PTSD as a novel target for secondary risk reduction.

Keywords: acute coronary syndrome, posttraumatic stress disorder, cardiovascular disease, emergency department, psychosocial factors, medication adherence

Over one million patients in the United States are hospitalized annually with acute coronary syndrome (ACS), including non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) (Benjamin et al., 2017). Despite improved survival rates in recent years due to improvements in medical care (McManus et al., 2011), recurrent cardiovascular event and mortality risk remains high for NSTEMI/UA patients (Sanchis-Gomar, Perez-Quilis, Leischik, & Lucia, 2016). ACS patients are not only at risk for recurrent cardiac events and mortality. For many, the ACS is a frightening experience associated with significant pain and fear of dying (von Känel et al., 2011; Whitehead, Strike, Perkins-Porras, & Steptoe, 2005), and may induce long-lasting symptoms of post-traumatic stress disorder (PTSD) (Abbas et al., 2009), a psychiatric disorder characterized by psychological distress and impaired functioning (Cohen et al., 2009).

Investigating the link between ACS-induced PTSD and recurrence of cardiovascular events

PTSD is diagnosed when an individual experiences four categories of symptoms after exposure to a life-threatening traumatic event: persistent re-experiencing of the event; efforts to avoid stimuli related to the event; negative alterations in cognition and mood; and alterations in arousals and reactivity (American Psychiatric Association, 2013). In 1994, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) included life-threatening illnesses as a type of traumatic event that could induce PTSD (American Psychiatric Association, 1994). Since then, a growing number of researchers have evaluated the incidence of PTSD among ACS survivors (Spindler & Pedersen, 2005; Tedstone & Tarrier, 2003). A meta-analysis of 24 studies revealed that ACS-induced PTSD is common, present in 12% (95% confidence interval [CI], 9%-16%) of ACS survivors (Edmondson et al., 2012).

ACS-induced PTSD may also increase cardiovascular risk. An emerging body of literature shows that PTSD due to non-medical events is associated with increased incidence of coronary heart disease (CHD) in initially healthy adults (Edmondson & Cohen, 2013; Edmondson, Kronish, Shaffer, Falzon, & Burg, 2013; Vaccarino et al., 2013). Few studies, however, have assessed the impact of ACS-induced PTSD on subsequent prognosis. A recent meta-analysis comprised of just 3 studies and 617 total patients suggested that PTSD may double the risk of recurrent cardiovascular events/mortality (Edmondson et al., 2012). The evidence for this link requires further study, however, due to limitations in the supporting research to date. First, the number of studies in this preliminary meta-analysis is quite low. Second, one of the three studies had a non-significant increased risk for the overall measure of PTSD symptoms and instead showed an association specific to the intrusions subscale of PTSD (Edmondson et al., 2011). Third, one of the studies had a particularly small sample size ($N = 73$) (Shemesh et al., 2004).

Several mechanisms have been proposed to explain how PTSD could increase cardiovascular risk. Among the most promising are behavioral pathways. Patients with PTSD are typically burdened by intrusive memories of the traumatic event, and consciously or unconsciously attempt to avoid reminders of this experience. Thus, when PTSD is induced by an ACS, survivors might avoid taking the medications that remind them of their heart disease. In support of this hypothesis, prior studies have shown that patients with stroke-induced PTSD report increased concerns about their medications but not decreased awareness of their necessity for secondary prevention, suggesting an ambivalent attitude towards medications which could be another manifestation of an avoidance phenomenon (Edmondson, Horowitz, Goldfinger, Fei, & Kronish, 2013). We and others have begun to explore whether ACS-induced PTSD is indeed

associated with lower adherence to cardioprotective medications. In a small study of 64 post-MI patients, patients with MI-induced PTSD were more likely to be non-adherent to aspirin as measured by platelet function testing (Shemesh et al., 2004). In a sample of 535 stroke survivors, we showed that those with “likely” stroke or transient ischemic attack (TIA)-induced PTSD had nearly 3 times the odds of self-reported non-adherence to medications compared to stroke survivors without PTSD (Kronish, Edmondson, Goldfinger, Fei, & Horowitz, 2012). We also showed in a cohort of primary care patients followed at Veterans Administration clinics that those with PTSD diagnosis were more likely to report missing or skipping their medications, consistent with our avoidance hypothesis (Kronish, Edmondson, Li, & Cohen, 2012). Not all studies, however, have found an independent association between PTSD and medication adherence. In a cohort of patients with stable CHD, for example, PTSD was not associated with medication adherence after adjusting for depression (Zen, Whooley, Zhao, & Cohen, 2012).

Many patients who present to the ED with acute chest pain are ultimately ruled out for ACS. A number of studies have described the psychological impact of ACS (Cohen, Edmondson, & Kronish, 2015). Much less is known about the experience of patients who present to the ED with probable ACS, but who subsequently rule out after diagnostic testing. Of all the patients who present to the ED with ACS-like symptoms (e.g., chest pain, shortness of breath, left arm pain, in the presence of documented risk factors for ACS), less than half are ultimately diagnosed with an ACS (Goodacre et al., 2005). Most patients who rule out for ACS receive non-life-threatening diagnoses for their presenting symptoms, such as musculoskeletal pain or gastroesophageal reflux disorders, while others do not receive any specific diagnosis (Chambers, Marks, & Hunter, 2015). Prior studies suggest that patients with a non-cardiac etiology for their ACS-like symptoms have increased health care utilization and costs, but they are not at increased

risk of subsequent cardiovascular events (Fagring et al., 2010). Because of the relatively benign medical prognosis for patients who rule out for ACS, physicians may see little cause for concern once patients rule out. However, from the point of view of the patient, the experience of presenting to the hospital with ACS symptoms may still be traumatic, irrespective of the final diagnosis they receive. Indeed, patients often do not know whether their ACS symptoms were ultimately diagnosed as ACS (Yasaitis, Berkman, & Chandra, 2015). PTSD is now commonly understood to be induced by the perception of life threat during a traumatic event, regardless of the objective risk, particularly for potentially life threatening medical events (Laubmeier & Zakowski, 2004). Accordingly, patients who rule out for ACS may still be at risk for developing PTSD due to the event. Many of these patients have underlying CVD risk factors that led to concern for ACS in the first place, and such patients who develop PTSD symptoms may similarly be at risk for avoiding their cardiovascular medications. No study has tested whether PTSD induced by a suspected but unconfirmed ACS can influence medication adherence or CVD risk and mortality.

Risk factors for ACS-induced PTSD

Although risk factors for PTSD due to stereotypically PTSD-inducing events such as combat and assault are well described, less is known about the factors that predict PTSD after ACS. Identifying risk factors is necessary for guiding development of interventions to prevent ACS-induced PTSD in patients at highest risk. If PTSD also increases secondary CVD risk, then interventions that prevent PTSD may have collateral benefits on reducing CVD events and mortality in ACS patients as well.

There are many factors during the initial ED visit that can induce stress and may influence the development of PTSD. These can be subsumed under three categories:

environmental, personal, and social, each of which is assessed in the present study. To our knowledge, few prior studies have assessed the role of these ED factors in predicting ACS-induced PTSD. Accordingly, there is a need to comprehensively assess the role of the ED environment (i.e., crowding, wait time, exposure to critical care), reactivity of the patient (physiological or psychological), and interpersonal aspects of the patient experience (doctor-patient communication, social support) with respect to subsequent ACS-induced PTSD risk. Each set of factors has putative and/or demonstrated links with PTSD and/or adverse health events.

A number of characteristics of the ED environment have been associated with psychological and cardiovascular outcomes. ED crowding tends to increase wait times and is a source of added stress among patients already experiencing alarming levels of cardiac distress (Kellermann, 2006). ED crowding has also been associated with increased risk of poor cardiac outcomes (Pines, Hollander, Localio, & Metlay, 2006) and one-year mortality (Shen & Hsia, 2011). In addition to long-term cardiac outcomes, ED crowding also predicts serious psychological distress in the form of more severe PTSD symptoms in NSTEMI/UA patients (Edmondson, Shimbo, Ye, Wyer, & Davidson, 2013). Exposure to potentially traumatic critical care procedures of other patients in the ED has also been associated with poorer cardiovascular outcomes (Fishman et al., 2006).

Individual differences in psychological and physiological reactivity among ACS patients in the ED are also essential factors to assess when considering the development of ACS-induced PTSD. Psychological responses to ACS such as anxiety during the event predict elevated PTSD symptoms (Rocha et al., 2008). In fact, fear of dying and helplessness are better predictors of who will develop PTSD than common metrics of the severity of the cardiac event (e.g., left

ventricular ejection fraction, number of coronary occlusions) (Guler et al., 2009). In non-ACS populations, physiological responses such as increased heart rate have also been associated with the development of PTSD (Zatzick et al., 2005).

Interpersonal factors constitute another set of ED factors that are putatively related to psychological and physical health outcomes. Lack of social support from family or friends in the ED predicts worse cardiovascular outcomes in the short term such as higher blood pressure and heart rate in response to stress (Thorsteinsson & James, 1999), and low social support is an established risk factor for PTSD in patients who experience myocardial infarction (Bennett, Owen, Koutsakis, & Bisson, 2002). Beyond the impact of friends and family, lower quality relationships between patients and doctors are associated with poorer health outcomes (Ong, De Haes, Hoos, & Lammes, 1995). Although research on the quality of patient-doctor communication in the ED and subsequent PTSD is limited, it is likely that poor patient-doctor communication is relevant to psychological outcomes (Chang, Sumner, Haerizadeh, Carter, & Edmondson, 2016).

Given the multiple variables and pathways that may contribute to the development of ACS-induced PTSD in the acute care environment, the efficient and systematic evaluation of these potential relationships raises numerous methodological challenges. The assessment of ACS-induced PTSD and its associated psychological and cardiovascular outcomes involves the collection of data across multiple timepoints and clinical contexts (e.g., ED, inpatient setting, at-home treatment). Difficulties may also exist for the efficient enrollment and follow-up of patients treated for life-threatening disease in the often chaotic ED setting. Additionally, it is necessary to collect time-sensitive, ecological information from patients while they are still in the ED setting being evaluated for ACS. Interviewing patients while undergoing ACS evaluation in the ED

allows one to assess ED, patient, and interpersonal factors during that heightened period of uncertainty that may influence patients' long-term psychological adjustment.

In this paper, we describe the design and methods of the Reactions to Acute Care and Hospitalizations (ReACH) study, a prospective observational cohort study that enrolls patients being evaluated in the ED for ACS, and follows them for 1 year to PTSD and CVD/mortality outcomes. The ReACH study tests a theoretical model in which ED factors contribute to the development of post-traumatic stress disorder (PTSD), which may in turn influence prognosis, including risk for cardiac event recurrence and mortality. We also test one potential mechanism by which PTSD symptoms may increase risk for health events: poor medication adherence (see Figure 1 for a depiction of the framework of tested associations emerging over time).

The study aims are as follows: (1) to test whether suspected ACS-induced PTSD is associated with increased risk of mortality and recurrent major adverse cardiac events (MACE) at 1 year; (2) to determine whether electronically-measured medication nonadherence mediates any association of suspected ACS-induced PTSD with CVD risk; (3) to identify predictors of suspected ACS-induced PTSD that are related to the patient, the physicians, and the ED environment. Not all patients who are initially evaluated for ACS in the ED will later be confirmed to have ACS. Therefore our study data provide an opportunity to determine whether patients who “rule out” for ACS are similarly at increased risk of PTSD and adverse CVD outcomes as patients with confirmed ACS. Thus, an exploratory aim of the study is to test whether risk for these adverse outcomes differs according to true ACS vs. ACS rule-out status. By sharing our study design, we hope to present an efficient and efficacious model for conducting prospective observational work in acute care environments such as the ED.

Methods

Participants enrolled in this study are patients who present to the Columbia-New York Presbyterian Hospital ED with chest pain and a suspected diagnosis of NSTEMI or UA during initial presentation (see below for inclusion/exclusion criteria). Patients with STEMI were not enrolled as these patients are typically rushed to the cardiac catheterization lab before ED assessments can be completed, a key component of the study design. Columbia-New York Presbyterian Hospital is a quaternary academic medical center serving a dense urban area. The hospital has over 100,000 ED visits annually.

Potential participants are screened by a team of trained research assistants (RAs) based on the ED E-Track electronic record and physician referrals. After the researchers explain the study and answers any questions that arise, patients who choose to participate provide informed consent. All study protocols have been approved by the Columbia University Medical Center Institutional Review Board. The first phase of the study occurs in the ED (Time 1; T1) and consists of identification of potential participants, informed consent for the main study (and the ancillary, medication adherence study if eligible), and brief interviews about their cardiac event symptoms and current perceptions of personal threat related to the ACS event and the ED itself. Medical record numbers of enrolled participants are recorded so that patients can be tracked as they are transferred to an inpatient bed. The second phase of the study occurs after participants are admitted to inpatient care (Time 2; T2), and consists of the remainder of the baseline interview about psychosocial and interpersonal factors. For participants who are discharged prior to completing the second phase of the baseline questionnaire, the interview is completed by telephone. The third through fifth phases of the study are telephone interviews conducted 1 month (Time 3; T3), 6 months (Time 4; T4), and 12 months (Time 5; T5) after enrollment with participants or their close contacts. The 1-month interview assesses PTSD symptoms using the

gold standard screening instrument for PTSD, hospital readmission/mortality (family report), as well as extent of and reasons for cardiovascular medication nonadherence. The 6-month and 12-month telephone interviews are largely identical to the 1-month interview. The ancillary adherence study consists of up to 6 months of electronically-monitored cardiovascular medication adherence beginning at discharge from the hospital; patients are asked to monitor aspirin or if not prescribed then another cardiovascular medication from a bottle with an electronic pillcap. Figure 2 presents the study timetable for the main and ancillary studies.

Study recruitment began in November 2013. The target enrollment of 1,741 participants was achieved in May 2017 with a mean enrollment rate of 2.27 patients per day ($SD = 1.35$). The last of the 1,741 participants completed the 12-month phase of the study in May 2018. Of those 1,741 participants, 730 participants were sent electronic bottle cap (eCAP) devices (see Measures section below) for participation in the ancillary medication adherence study. (This number is necessarily considerably lower than the total number of participants in part because the ancillary study began after the main study.)

Eligibility criteria.

Eligible participants are English-or-Spanish-speaking adults aged 18 years or older who present to the ED with symptoms of a suspected NSTEMI or UA. NSTEMI is defined by a typical rise and gradual fall (troponin levels) or more rapid rise and fall (creatinine kinase MB levels) of biochemical markers of infarction with one of the following in the absence of ST elevations: (a) ST-segment depression; (b) T wave abnormalities; (c) ischemic symptoms without ST-segment depression or T wave abnormalities in the presence or absence of chest discomfort (unexplained nausea and vomiting or diaphoresis; persistent shortness of breath; unexplained weakness, dizziness, lightheadedness, or syncope). UA is defined by angina pectoris

(or equivalent type of ischemic discomfort) with no biochemical evidence of MI and any of the following within the 6 weeks prior to admission: (a) angina occurring at rest that is prolonged, usually longer than 20 minutes; (b) new-onset angina of least class II severity according to the Canadian Cardiovascular Society criteria; (c) recent worsening of angina reflected by an increase in severity of at least class I to at least class II according to the Canadian Cardiovascular Society criteria.

Patients are excluded from participation if they are unable to complete the baseline assessment (ED and inpatient study phases) within 1 week of hospitalization, do not have reliable phone or email access, are deemed unable to comply with the protocol by self-selection or by indicating during screening an inability to complete all tasks (due to cognitive impairment or current alcohol or substance abuse problems), are deemed to need psychiatric intervention within 72 hours, are prisoners, or are unavailable for follow-up (e.g., life expectancy < 1 year, about to leave United States). Patients are excluded from the ancillary medication adherence study if they are not prescribed aspirin or another cardiovascular medication, are unable to self-administer medications (e.g., live in nursing home), or are concerned that taking a cardiovascular medication from a separate pill bottle will disrupt their medication-taking habits (e.g., patients that prefer to use only pillboxes).

Measures.

Phase 1: In the ED (T1).

After consenting patients provide authorization to release medical records, they then provide demographic information and complete an interview-administered questionnaire assessing perceptions of ED crowding and the ACS event, including assessments of current threat perceptions. Participants' physiological arousal is assessed using each patient's mean and

standard deviation of heart rate, blood pressure, and respiratory rate using ED medical record data. Current threat perceptions in the ED are assessed by participant self-report (e.g., “I am worried that I am dying,” “I feel helpless,” “I think this event will have a big impact on my life”; Ozer, Best, Lipsey, & Weiss, 2003). This measure of ED threat perceptions demonstrates evidence of convergent validity in that it correlates positively with perceptions of relevant ED factors (stress, crowding), and it has shown good internal consistency reliability and stability over time (Cornelius et al., 2018). Finally, intensity and duration of pain are self-reported. Electronic records are used to objectively assess ED variables, and ED crowding metrics such as the Emergency Department Work Index (EDWIN) and National Emergency Department Overcrowding Scale (NEDOCS) are calculated (McCarthy et al., 2008; Weiss et al., 2005). Each patient’s exposure to critical care is recorded, including any ED trauma activations and ED deaths that occur during each participant’s recorded time in the ED.

Phase 2: Inpatient (T2).

Characteristics of doctor-patient communication during ED evaluation are assessed during the inpatient interview using The Interpersonal Processes of Care Survey (Stewart, Nápoles-Springer, Gregorich, & Santoyo-Olsson, 2007). Patient-doctor discordances in race, ethnicity, and first language are assessed. Social support in the ED is assessed by participant report of who was present with them in the ED, as well as the degree to which the interpersonal support provided to them was appropriate for the event, whether the patient chose to receive the support, and the quality of the participant’s relationship with the support provider. Due to the study’s specific focus on the consequences of ACS-induced PTSD, previous PTSD not due to NSTEMI/UA is also assessed to avoid potential confounds. This is measured with the PTSD Checklist-Civilian (PCL-C; Weathers, Litz, Herman, Huska, & Keane, 1993). The PCL-C has

been shown evidence for appropriate convergent and discriminant validity, excellent internal consistency reliability, and adequate test-test reliability (Ruggiero, Ben, Scotti, & Rabalais, 2003). Furthermore, given the unique variance in health outcomes explained by depressive symptoms during hospitalization, depressive symptoms are measured using the Patient Health Questionnaire (PHQ-8; Kroenke et al., 2009) to include as a control variable in primary outcome analyses. This measure has been shown to have adequate validity and internal consistency reliability in previous samples (Kroenke et al., 2009; Pressler et al., 2011). Patients also complete the Acute Stress Disorder Scale (ASDS; Bryant, Moulds, & Guthrie, 2000) to measure early symptoms of distress that may indicate risk for developing PTSD. This measure has been demonstrated to be a sensitive predictor of development of subsequent PTSD and to have excellent internal consistency reliability and strong test-retest reliability (Bryant et al., 2000). Additionally, the following items and scales are collected at T2: recall of ED threat perceptions (parallel to ED threat perception items administered at T1), the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989), the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1994), the International Physical Activity Questionnaire (IPAQ; Craig et al., 2003), and the Life Events Checklist (LEC; Gray, Litz, Hsu, & Lombardo, 2004).

Immediately after discharge, patients enrolled in the ancillary medication adherence study are mailed an electronic bottle cap (eCAP, Information Mediary Corp., Ottawa, Canada) that automatically records openings of medication bottles. For up to 6 months after the initial ACS event, patients are expected to take aspirin or one of their other cardiovascular medications, from a bottle with an eCAP. Participants are contacted to remind them to mail back the eCAP

bottle, and for the purposes of this observational study, no counseling about medication adherence is administered.

Post-discharge follow-up (T3 - T5).

The primary outcomes for this observational study are ACS recurrence and mortality. Proactive medical record searches are conducted daily for all study participants to identify new ED visits and/or hospital readmissions. Suspected ACS events are also identified by participant self-report and then confirmed using hospital records with an adjudication process involving a research nurse and 2 study cardiologists. All-cause mortality is queried by calling alternative contacts, and mortality is confirmed by automatic checking of the social security death index (SSDI) as part of routine management of electronic medical records. Additionally, in-hospital deaths are confirmed via hospitalization records.

The primary study exposure of interest is suspected ACS-induced PTSD. During the 1-month telephone interview, PTSD symptoms related to the suspected ACS event and its treatment are assessed using the PCL-specific for the cardiac event.

The primary mechanism for the hypothesized association of PTSD with ACS recurrence and mortality risk is electronically-measured medication nonadherence. The extent of and reasons for nonadherence are also assessed by self-report. Extent of nonadherence to cardiovascular medications was assessed during the 1-month telephone interview (T3) using a single item from the Coronary Artery Risk Development in Young Adults (CARDIA) study, “In the past month, how often did you take your heart medications as your doctor prescribed?” scored from 1, “less than half of the time (< 50%),” to 5, “all of the time (100%)” (Cutter et al., 1991), and by using a 3-item scale psychometrically developed by Voils and colleagues (Voils et al., 2012). Aversive cognitions towards cardiovascular medications were assessed at 1 month

(T3) by asking patients: “How often did” 1) “you miss your heart medication because you did not want to be reminded of your heart problem”, 2) “thinking about your heart medication make you feel nervous or anxious”, and 3) “thinking about your heart medication make you think about your risk for future heart problems.” Patients responded using a 5-point Likert scale scored from 1, “never,” to 5, “all of the time.” These items were based directly on the Enduring Somatic Threat theory framework (Edmondson, 2014).

Statistical approach.

To test whether suspected ACS-induced PTSD is associated with increased secondary risk at 1 year, we will use a Cox proportional hazards model with 1-month PTSD assessment ($PCL \geq 33$) predicting subsequent acute coronary heart disease event (non-fatal myocardial infarction or hospitalization for unstable angina) or all-cause mortality with adjustment for demographic and clinical variables, as well as depression ($PHQ \geq 10$) (Kroenke et al., 2009). The PCL cut point of 33 is used due to its being in the middle of the lower (30) and upper (35) bounds of the range of cut points suggested by the National Center for PTSD for a sample of civilians in a primary care setting or the general population, and was the estimated cutoff associated with increased recurrence risk in the 2013 meta-analysis. If there is a statistically significant association between suspected ACS-induced PTSD and secondary risk, we will determine whether medication nonadherence partially mediates the association between PTSD symptoms and MACE/ACM by running a mediation test with bootstrapping. Specifically, the predictor in this model will be PTSD symptoms assessed at the 1-month interview (T3), the proposed mediator will be electronic adherence data measured prior to the 1-month interview, and the outcome will be occurrence of the secondary risk health events (described above) after the 1-month interview until the end of the study. Regarding the third aim, multiple regression

models will be used to test the associations of patient, physician, and ED factors with subsequent 1-month PTSD symptoms induced by suspected ACS. As an exploratory aim, we will determine whether patients who “rule out” for ACS are at similarly increased risk of PTSD and adverse CVD outcomes in a Cox proportional hazards regression that compares survival functions for patients with confirmed ACS versus those who rule out for ACS at baseline.

Sample size determination.

Sample for testing links among ED factors, PTSD, risk of mortality and recurrent MACE.

We expected that 8% to 10% of participants would have a cardiac event recurrence/ACM event during the year following their index cardiac event. In our previous study, 10.4% had a cardiac event recurrence/ACM in the year following their index cardiac event. The sample size calculations are based on the conservative estimate of 8% cardiac event recurrence/ACM and a 2-tailed test at $\alpha=0.05$. Although we anticipated higher retention rates, to provide conservative sample size estimates, we allowed for 15% of participants to be unavailable for follow-up at 1 year (although medical record data for the primary outcome will be available for almost all participants). Based on prior data, we anticipated that 10% to 15% of participants would have PTSD at the 1-month follow-up contact. Based on these estimates, we planned to enroll 1,741 participants, which we expect to yield a final sample size of 1,488 or larger. Of the 1,741, we expected that 1,567 would complete the 1-month assessment. For the association between PTSD incidence at 1 month and a new cardiovascular event/ACM in the 1 year after enrollment (hypothesis 1), the detectable hazard ratio is 2.39 assuming that the incidence of PTSD is 15% at 1 month.

Preliminary results

Table 1 shows the baseline characteristics of patients recruited to date. Participants are racially and ethnically diverse. They demonstrate a range of severity of their ACS conditions, medical comorbidities, prior PTSD symptoms, and depressive symptoms. Overall, the sample is characterized by a wide age range, an expected sex distribution, substantial racial/ethnic diversity, low socioeconomic status, and high medical and psychological comorbidity burden.

Discussion

Given that hundreds of thousands of patients present for ACS each year, it is imperative to determine the extent to which ACS is associated with the development of PTSD and the extent to which this medical event-induced form of PTSD—in addition to being psychologically debilitating in its own right—is associated prospectively with increased risk of CVD event recurrence and mortality. Then, as a next step, it is essential to examine the mechanisms by which ACS-induced PTSD contributes to secondary risk. One key mechanism may be nonadherence to secondary prevention medications.

The study design has several strengths. First, it benefits from assessing acute stress exposure at the critical time of the ED admission without causing additional, undue burden to patients or altering the course of care or medication habits. Second, it includes a large and diverse longitudinal cohort, which improves generalizability of findings to the larger population of NSTEMI/UA patients across the United States as well as to the even larger number of patients who present to the ED with ACS symptoms but are ruled out, particularly in racially and ethnically diverse, low-SES settings. Third, there is a high quality of measurement for all key variables, including the adjudication of ACS status by expert cardiologists, the objective measure of cardiovascular medication adherence, and attention to potential confounds (i.e., non-ACS-induced PTSD and depression at baseline). Fourth, the study is designed to identify factors that

are most important to target for future interventions designed to offset the expected risk of cardiac recurrence, mortality, and PTSD in NSTEMI/UA patients.

The study has some limitations. Evidence of mediation does not definitively prove causality. That is, a causal pathway is not proven if their nonadherence mediates the association between PTSD symptoms and health outcomes. Nevertheless, the longitudinal design and attention to confounds (e.g., PTSD symptoms unrelated to the ACS event, ACS severity, demographic characteristics) lends credence to a causal interpretation of findings. A second limitation is that the study's 12-month design precludes the possibility of following these same patients for longer periods after their potentially traumatic experience in the ED. Nevertheless, research suggests that ED factors do influence medical outcomes within 1 year (Pines et al., 2009; Shen & Hsia, 2011). A third limitation is that PTSD is assessed only by self-reported measures and not by psychiatric interview in this study. However, with respect to the gold standard measure for assessing PTSD, the clinician-administered PTSD scale (CAPS; Blake, 1990), the PCL is a PTSD screening tool that has a valid symptom severity index (Ruggiero et al., 2003). Furthermore, if PCL symptoms predict increased cardiac risk, then there may be reason for physicians to use this easily administered measure during the course of clinical care for their ACS patients, irrespective of whether patients meet the diagnostic threshold for PTSD. Finally, it should be noted that the present study focuses on medication adherence, which is just one of several potential mechanisms by which ACS-induced PTSD may influence health outcomes. Other examples of potential mechanisms include autonomic imbalance, low physical activity, and disrupted sleep (for a review, see Edmondson & von Kanel, 2017).

Conclusion.

This prospective observational study will be the most definitive study to date of PTSD as a psychological reaction to an acute cardiac event, and the short-term psychological outcomes and long-term cardiovascular outcomes associated with PTSD, including subsequent MI and death. It will also provide insight into the ED and hospital characteristics that may influence the development of PTSD after acute cardiovascular events. In providing an overview of our study design and methods, we hope to provide future investigators with a model of the assessment of psychological and secondary cardiovascular risk following ACS events in an acute setting. If our hypotheses are supported, we will have identified an important modifiable secondary risk factor (ACS-induced PTSD) that may be preventable through changes to the way patients are evaluated and treated in the ED and hospital. Although many ED factors are largely modifiable, no accepted guidelines exist for managing ED factors that can influence psychological outcomes. Further, these results may shed light on the pernicious problem of nonadherence to secondary prevention cardiovascular medications, and point to novel psychologically-oriented interventions to improve adherence and secondary risk (as well as quality of life) in survivors of acute cardiovascular events.

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Table 1. Unless otherwise indicated, data are expressed as number (percentage) of patients.

Table 1

Demographic and clinical participant characteristics.

Demographic information	
Age, mean in years (SD)	60.54 (13.28)
Female	818 (47.0%)
Black	397 (24.0%)
Hispanic	1,003 (59.4%)
Education (completed high school)	1,137 (65.4%)
Current partner	751 (43.5%)
Current health insurance	1,537 (89.5%)
Medical information	
ACS confirmed: NSTEMI	311 (17.9%)
ACS confirmed: UA	230 (13.2%)
Prior cardiac event*	537 (30.8%)
Atherosclerotic disease	199 (11.7%)
GRACE score, mean (SD)	93.80 (29.98)
Charlson comorbidity index, mean (SD)	1.78 (1.98)
Psychiatric conditions at baseline	
Non-ACS-induced PTSD symptoms, mean (SD)	26.81 (13.71)
Baseline depressive symptoms, mean (SD)	6.61 (5.90)

*Record of prior confirmed myocardial infarction, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI)

Figure 1. Proposed theoretical model for investigating potential pathways connecting factors at the time of the initial emergency department (ED) visit in patients presenting with symptoms of acute coronary syndrome. ED factors in three domains predict subsequent post-traumatic stress disorder (PTSD), which predicts medical outcomes that may be partially mediated by changes in medication adherence.

Figure 2. Timetable for ReACH study procedures. The dotted vertical line indicates the transition between study phases occurring in the hospital versus at home. ED = emergency department. CVD = cardiovascular disease. ACS = acute coronary syndrome. ASD = acute stress disorder. PTSD = post-traumatic stress disorder. The eligibility screening and informed consent processes occur at the ED in the left-most time point on the timeline. Baseline assessments occur at the in-hospital ED (T1) and inpatient (T2) time points. Outcome variables are measured from the inpatient time point until up to 6 months for medication adherence and at the 1-month (T3), 6-month (T4), and 12-month (T5) time points for the other study outcome measures.

The impact of cardiac-induced post-traumatic stress disorder symptoms on cardiovascular outcomes: Design and rationale of the prospective observational Reactions to Acute Care and Hospitalizations (ReACH) study

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Abstract

Aims: As many as 1 in 8 acute coronary syndrome (ACS) patients develop posttraumatic stress disorder due to the ACS, and ACS-induced PTSD may increase secondary cardiovascular disease (CVD) risk. However, prior studies have been small and underpowered to test plausible behavioral or biological mechanisms of the hypothesized PTSD-secondary CVD risk association. In this paper, we describe the design and methods of a large prospective observational cohort study to estimate the prognostic significance of ACS-induced PTSD, mechanisms for its association with CVD risk, and emergency department (ED) factors that may increase PTSD risk, in a cohort of patients evaluated for acute coronary syndrome (ACS) in the ED of a large, urban academic medical center.

Methods: The Reactions to Acute Care and Hospitalization (ReACH) study will follow 1,741 racially, ethnically, and socioeconomically diverse patients initially presenting to the ED with ACS symptoms. Psychosocial factors are assessed at baseline. Medication adherence is monitored by electronic pill bottle (eCAP). Participants are contacted by phone at 1-, 6-, and 12-months post-hospitalization to assess PTSD symptoms, hospital readmission, and recurrent CVD events/mortality (proactively searched and confirmed by medical records).

Conclusion: This study will provide the most accurate estimates to date of PTSD's association with recurrent CVD events and mortality, and the mechanisms of that association. Further, it will provide estimates of the contribution of ED and hospital factors to PTSD risk in ACS patients. If our hypotheses are supported, we will have identified PTSD as a novel target for secondary risk reduction.

Keywords: acute coronary syndrome, posttraumatic stress disorder, cardiovascular disease, emergency department, psychosocial factors, medication adherence

Over one million patients in the United States are hospitalized annually with acute coronary syndrome (ACS), including non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina (UA) (Benjamin et al., 2017). Despite improved survival rates in recent years due to improvements in medical care (McManus et al., 2011), recurrent cardiovascular event and mortality risk remains high for NSTEMI/UA patients (Sanchis-Gomar, Perez-Quilis, Leischik, & Lucia, 2016). ACS patients are not only at risk for recurrent cardiac events and mortality. For many, the ACS is a frightening experience associated with significant pain and fear of dying (von Känel et al., 2011; Whitehead, Strike, Perkins-Porras, & Steptoe, 2005), and may induce long-lasting symptoms of post-traumatic stress disorder (PTSD) (Abbas et al., 2009), a psychiatric disorder characterized by psychological distress and impaired functioning (Cohen et al., 2009).

Investigating the link between ACS-induced PTSD and recurrence of cardiovascular events

PTSD is diagnosed when an individual experiences four categories of symptoms after exposure to a life-threatening traumatic event: persistent re-experiencing of the event; efforts to avoid stimuli related to the event; negative alterations in cognition and mood; and alterations in arousals and reactivity (American Psychiatric Association, 2013). In 1994, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) included life-threatening illnesses as a type of traumatic event that could induce PTSD (American Psychiatric Association, 1994). Since then, a growing number of researchers have evaluated the incidence of PTSD among ACS survivors (Spindler & Pedersen, 2005; Tedstone & Tarrier, 2003). A meta-analysis of 24 studies revealed that ACS-induced PTSD is common, present in 12% (95% confidence interval [CI], 9%-16%) of ACS survivors (Edmondson et al., 2012).

ACS-induced PTSD may also increase cardiovascular risk. An emerging body of literature shows that PTSD due to non-medical events is associated with increased incidence of coronary heart disease (CHD) in initially healthy adults (Edmondson & Cohen, 2013; Edmondson, Kronish, Shaffer, Falzon, & Burg, 2013; Vaccarino et al., 2013). Few studies, however, have assessed the impact of ACS-induced PTSD on subsequent prognosis. A recent meta-analysis comprised of just 3 studies and 617 total patients suggested that PTSD may double the risk of recurrent cardiovascular events/mortality (Edmondson et al., 2012). The evidence for this link requires further study, however, due to limitations in the supporting research to date. First, the number of studies in this preliminary meta-analysis is quite low. Second, one of the three studies had a non-significant increased risk for the overall measure of PTSD symptoms and instead showed an association specific to the intrusions subscale of PTSD (Edmondson et al., 2011). Third, one of the studies had a particularly small sample size ($N = 73$) (Shemesh et al., 2004).

Several mechanisms have been proposed to explain how PTSD could increase cardiovascular risk. Among the most promising are behavioral pathways. Patients with PTSD are typically burdened by intrusive memories of the traumatic event, and consciously or unconsciously attempt to avoid reminders of this experience. Thus, when PTSD is induced by an ACS, survivors might avoid taking the medications that remind them of their heart disease. In support of this hypothesis, prior studies have shown that patients with stroke-induced PTSD report increased concerns about their medications but not decreased awareness of their necessity for secondary prevention, suggesting an ambivalent attitude towards medications which could be another manifestation of an avoidance phenomenon (Edmondson, Horowitz, Goldfinger, Fei, & Kronish, 2013). We and others have begun to explore whether ACS-induced PTSD is indeed

associated with lower adherence to cardioprotective medications. In a small study of 64 post-MI patients, patients with MI-induced PTSD were more likely to be non-adherent to aspirin as measured by platelet function testing (Shemesh et al., 2004). In a sample of 535 stroke survivors, we showed that those with “likely” stroke or transient ischemic attack (TIA)-induced PTSD had nearly 3 times the odds of self-reported non-adherence to medications compared to stroke survivors without PTSD (Kronish, Edmondson, Goldfinger, Fei, & Horowitz, 2012). We also showed in a cohort of primary care patients followed at Veterans Administration clinics that those with PTSD diagnosis were more likely to report missing or skipping their medications, consistent with our avoidance hypothesis (Kronish, Edmondson, Li, & Cohen, 2012). Not all studies, however, have found an independent association between PTSD and medication adherence. In a cohort of patients with stable CHD, for example, PTSD was not associated with medication adherence after adjusting for depression (Zen, Whooley, Zhao, & Cohen, 2012).

Many patients who present to the ED with acute chest pain are ultimately ruled out for ACS. A number of studies have described the psychological impact of ACS (Cohen, Edmondson, & Kronish, 2015). Much less is known about the experience of patients who present to the ED with probable ACS, but who subsequently rule out after diagnostic testing. Of all the patients who present to the ED with ACS-like symptoms (e.g., chest pain, shortness of breath, left arm pain, in the presence of documented risk factors for ACS), less than half are ultimately diagnosed with an ACS (Goodacre et al., 2005). Most patients who rule out for ACS receive non-life-threatening diagnoses for their presenting symptoms, such as musculoskeletal pain or gastroesophageal reflux disorders, while others do not receive any specific diagnosis (Chambers, Marks, & Hunter, 2015). Prior studies suggest that patients with a non-cardiac etiology for their ACS-like symptoms have increased health care utilization and costs, but they are not at increased

risk of subsequent cardiovascular events (Fagring et al., 2010). Because of the relatively benign medical prognosis for patients who rule out for ACS, physicians may see little cause for concern once patients rule out. However, from the point of view of the patient, the experience of presenting to the hospital with ACS symptoms may still be traumatic, irrespective of the final diagnosis they receive. Indeed, patients often do not know whether their ACS symptoms were ultimately diagnosed as ACS (Yasaitis, Berkman, & Chandra, 2015). PTSD is now commonly understood to be induced by the perception of life threat during a traumatic event, regardless of the objective risk, particularly for potentially life threatening medical events (Laubmeier & Zakowski, 2004). Accordingly, patients who rule out for ACS may still be at risk for developing PTSD due to the event. Many of these patients have underlying CVD risk factors that led to concern for ACS in the first place, and such patients who develop PTSD symptoms may similarly be at risk for avoiding their cardiovascular medications. No study has tested whether PTSD induced by a suspected but unconfirmed ACS can influence medication adherence or CVD risk and mortality.

Risk factors for ACS-induced PTSD

Although risk factors for PTSD due to stereotypically PTSD-inducing events such as combat and assault are well described, less is known about the factors that predict PTSD after ACS. Identifying risk factors is necessary for guiding development of interventions to prevent ACS-induced PTSD in patients at highest risk. If PTSD also increases secondary CVD risk, then interventions that prevent PTSD may have collateral benefits on reducing CVD events and mortality in ACS patients as well.

There are many factors during the initial ED visit that can induce stress and may influence the development of PTSD. These can be subsumed under three categories:

environmental, personal, and social, each of which is assessed in the present study. To our knowledge, few prior studies have assessed the role of these ED factors in predicting ACS-induced PTSD. Accordingly, there is a need to comprehensively assess the role of the ED environment (i.e., crowding, wait time, exposure to critical care), reactivity of the patient (physiological or psychological), and interpersonal aspects of the patient experience (doctor-patient communication, social support) with respect to subsequent ACS-induced PTSD risk. Each set of factors has putative and/or demonstrated links with PTSD and/or adverse health events.

A number of characteristics of the ED environment have been associated with psychological and cardiovascular outcomes. ED crowding tends to increase wait times and is a source of added stress among patients already experiencing alarming levels of cardiac distress (Kellermann, 2006). ED crowding has also been associated with increased risk of poor cardiac outcomes (Pines, Hollander, Localio, & Metlay, 2006) and one-year mortality (Shen & Hsia, 2011). In addition to long-term cardiac outcomes, ED crowding also predicts serious psychological distress in the form of more severe PTSD symptoms in NSTEMI/UA patients (Edmondson, Shimbo, Ye, Wyer, & Davidson, 2013). Exposure to potentially traumatic critical care procedures of other patients in the ED has also been associated with poorer cardiovascular outcomes (Fishman et al., 2006).

Individual differences in psychological and physiological reactivity among ACS patients in the ED are also essential factors to assess when considering the development of ACS-induced PTSD. Psychological responses to ACS such as anxiety during the event predict elevated PTSD symptoms (Rocha et al., 2008). In fact, fear of dying and helplessness are better predictors of who will develop PTSD than common metrics of the severity of the cardiac event (e.g., left

ventricular ejection fraction, number of coronary occlusions) (Guler et al., 2009). In non-ACS populations, physiological responses such as increased heart rate have also been associated with the development of PTSD (Zatzick et al., 2005).

Interpersonal factors constitute another set of ED factors that are putatively related to psychological and physical health outcomes. Lack of social support from family or friends in the ED predicts worse cardiovascular outcomes in the short term such as higher blood pressure and heart rate in response to stress (Thorsteinsson & James, 1999), and low social support is an established risk factor for PTSD in patients who experience myocardial infarction (Bennett, Owen, Koutsakis, & Bisson, 2002). Beyond the impact of friends and family, lower quality relationships between patients and doctors are associated with poorer health outcomes (Ong, De Haes, Hoos, & Lammes, 1995). Although research on the quality of patient-doctor communication in the ED and subsequent PTSD is limited, it is likely that poor patient-doctor communication is relevant to psychological outcomes (Chang, Sumner, Haerizadeh, Carter, & Edmondson, 2016).

Given the multiple variables and pathways that may contribute to the development of ACS-induced PTSD in the acute care environment, the efficient and systematic evaluation of these potential relationships raises numerous methodological challenges. The assessment of ACS-induced PTSD and its associated psychological and cardiovascular outcomes involves the collection of data across multiple timepoints and clinical contexts (e.g., ED, inpatient setting, at-home treatment). Difficulties may also exist for the efficient enrollment and follow-up of patients treated for life-threatening disease in the often chaotic ED setting. Additionally, it is necessary to collect time-sensitive, ecological information from patients while they are still in the ED setting being evaluated for ACS. Interviewing patients while undergoing ACS evaluation in the ED

allows one to assess ED, patient, and interpersonal factors during that heightened period of uncertainty that may influence patients' long-term psychological adjustment.

In this paper, we describe the design and methods of the Reactions to Acute Care and Hospitalizations (ReACH) study, a prospective observational cohort study that enrolls patients being evaluated in the ED for ACS, and follows them for 1 year to PTSD and CVD/mortality outcomes. The ReACH study tests a theoretical model in which ED factors contribute to the development of post-traumatic stress disorder (PTSD), which may in turn influence prognosis, including risk for cardiac event recurrence and mortality. We also test one potential mechanism by which PTSD symptoms may increase risk for health events: poor medication adherence (see Figure 1 for a depiction of the framework of tested associations emerging over time).

The study aims are as follows: (1) to test whether suspected ACS-induced PTSD is associated with increased risk of mortality and recurrent major adverse cardiac events (MACE) at 1 year; (2) to determine whether electronically-measured medication nonadherence mediates any association of suspected ACS-induced PTSD with CVD risk; (3) to identify predictors of suspected ACS-induced PTSD that are related to the patient, the physicians, and the ED environment; (4) and to determine whether patients who “rule out” for ACS are similarly at increased risk of PTSD and adverse CVD outcomes. By sharing our study design, we hope to present an efficient and efficacious model for conducting prospective observational work in acute care environments such as the ED.

Methods

Participants enrolled in this study are patients who present to the Columbia-New York Presbyterian Hospital ED with chest pain and a suspected diagnosis of NSTEMI or UA during initial presentation (see below for inclusion/exclusion criteria). Patients with STEMI were not

enrolled as these patients are typically rushed to the cardiac catheterization lab before ED assessments can be completed, a key component of the study design. Columbia-New York Presbyterian Hospital is a quaternary academic medical center serving a dense urban area. The hospital has over 100,000 ED visits annually.

Potential participants are screened by a team of trained research assistants (RAs) based on the ED E-Track electronic record and physician referrals. The first phase of the study occurs in the ED and consists of identification of potential participants, informed consent for the main study (and the ancillary, medication adherence study if eligible), and brief interviews about their cardiac event symptoms and current perceptions of personal threat related to the ACS event and the ED itself. Medical record numbers of enrolled participants are recorded so that patients can be tracked as they are transferred to an inpatient bed. The second phase of the study occurs after participants are admitted to inpatient care, and consists of the remainder of the baseline interview about psychosocial and interpersonal factors. For participants who are discharged prior to completing the second phase of the baseline questionnaire, the interview is completed by telephone. The third through fifth phases of the study are telephone interviews conducted 1 month, 6 months, and 12 months after enrollment with participants or their close contacts. The 1-month interview assesses PTSD symptoms using the gold standard screening instrument for PTSD, hospital readmission/mortality (family report), as well as extent of and reasons for cardiovascular medication nonadherence. The 6-month and 12-month telephone interviews are largely identical to the 1-month interview. The ancillary adherence study consists of up to 6 months of electronically-monitored cardiovascular medication adherence beginning at discharge from the hospital; patients are asked to monitor aspirin or if not prescribed then another

cardiovascular medication from a bottle with an electronic pillcap. Figure 2 presents the study timetable for the main and ancillary studies.

Study recruitment began in November 2013. The target enrollment of 1,741 participants was achieved in May 2017 with a mean enrollment rate of 2.27 patients per day ($SD = 1.35$). The last of the 1,741 participants will complete the 12-month phase of the study in May 2018.

Eligibility criteria.

Eligible participants are English-or-Spanish-speaking adults aged 18 years or older who present to the ED with symptoms of a suspected NSTEMI or UA. NSTEMI is defined by a typical rise and gradual fall (troponin levels) or more rapid rise and fall (creatinine kinase MB levels) of biochemical markers of infarction with one of the following in the absence of ST elevations: (a) ST-segment depression; (b) T wave abnormalities; (c) ischemic symptoms without ST-segment depression or T wave abnormalities in the presence or absence of chest discomfort (unexplained nausea and vomiting or diaphoresis; persistent shortness of breath; unexplained weakness, dizziness, lightheadedness, or syncope). UA is defined by angina pectoris (or equivalent type of ischemic discomfort) with no biochemical evidence of MI and any of the following within the 6 weeks prior to admission: (a) angina occurring at rest that is prolonged, usually longer than 20 minutes; (b) new-onset angina of least class II severity according to the Canadian Cardiovascular Society criteria; (c) recent worsening of angina reflected by an increase in severity of at least class I to at least class II according to the Canadian Cardiovascular Society criteria.

Patients are excluded from participation if they are unable to complete the baseline assessment (ED and inpatient study phases) within 1 week of hospitalization, do not have reliable phone or email access, are deemed unable to comply with the protocol by self-selection

or by indicating during screening an inability to complete all tasks (due to cognitive impairment or current alcohol or substance abuse problems), are deemed to need psychiatric intervention within 72 hours, are prisoners, or are unavailable for follow-up (e.g., life expectancy < 1 year, about to leave United States). Patients are excluded from the ancillary medication adherence study if they are not prescribed aspirin or another cardiovascular medication, are unable to self-administer medications (e.g., live in nursing home), or are concerned that taking a cardiovascular medication from a separate pill bottle will disrupt their medication-taking habits (e.g., patients that prefer to use only pillboxes).

Measures.

Phase 1: In the ED.

Consenting patients complete an interview-administered questionnaire assessing perceptions of ED crowding and the ACS event, including assessments of current threat perceptions and pain level. Participants' physiological arousal is assessed using each patient's mean and standard deviation of heart rate, blood pressure, and respiratory rate using ED medical record data. Current threat perceptions in the ED are assessed by participant self-report (e.g., "I am worried that I am dying," "I feel helpless," "I think this event will have a big impact on my life").(Ozer, Best, Lipsey, & Weiss, 2003) Finally, intensity and duration of pain are self-reported. Electronic records are used to objectively assess ED variables, and ED crowding metrics such as the Emergency Department Work Index (EDWIN) and National Emergency Department Overcrowding Scale (NEDOCS) are calculated.(McCarthy et al., 2008; Weiss et al., 2005) Each patient's exposure to critical care is recorded, including any ED trauma activations and ED deaths that occur during each participant's recorded time in the ED.

Phase 2: Inpatient.

The quality of doctor-patient communication during ED evaluation is measured during the inpatient interview using The Interpersonal Processes of Care Survey (Stewart, Nápoles-Springer, Gregorich, & Santoyo-Olsson, 2007). Patient-doctor discordances in race, ethnicity, and first language are assessed. Social support in the ED is assessed by participant report of who was present with them in the ED, as well as the degree to which the interpersonal support provided to them was appropriate for the event, whether the patient chose to receive the support, and the quality of the participant's relationship with the support provider. Due to the study's specific focus on the consequences of ACS-induced PTSD, previous PTSD not due to NSTEMI/UA is also assessed to avoid potential confounds. This is measured with the PTSD Checklist-Civilian (PCL-C; Weathers, Litz, Herman, Huska, & Keane, 1993). Furthermore, given the unique variance in health outcomes explained by depressive symptoms during hospitalization, depressive symptoms are measured using the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & ERBAUGH, 1961) to include as a control variable in primary outcome analyses.

Immediately after discharge, patients enrolled in the ancillary medication adherence study are mailed an electronic bottle cap (eCAP, Information Mediary Corp., Ottawa, Canada) that automatically records openings of medication bottles. For up to 6 months after the initial ACS event, patients are expected to take aspirin or one of their other cardiovascular medications, from a bottle with an eCAP. Participants are contacted to remind them to mail back the eCAP bottle, and for the purposes of this observational study, no counseling about medication adherence is administered.

Post-discharge follow-up.

The primary outcomes for this observational study are ACS recurrence and mortality. Proactive medical record searches are conducted daily for all study participants to identify new ED visits and/or hospital readmissions. Suspected ACS events are also identified by participant self-report and then confirmed using hospital records with an adjudication process involving a research nurse and 2 study cardiologists. All-cause mortality is queried by calling alternative contacts, and mortality is confirmed by automatic checking of the social security death index (SSDI) as part of routine management of electronic medical records. Additionally, in-hospital deaths are confirmed via hospitalization records.

The primary study exposure of interest is suspected ACS-induced PTSD. During the 1-month telephone interview, PTSD symptoms related to the suspected ACS event and its treatment are assessed using the PCL-specific for the cardiac event.

The primary mechanism for the hypothesized association of PTSD with ACS recurrence and mortality risk is electronically-measured medication nonadherence. The extent of and reasons for nonadherence are also assessed by self-report. Extent of nonadherence to cardiovascular medications was assessed during the 1-month telephone interview using a single item from the Coronary Artery Risk Development in Young Adults (CARDIA) study, “In the past month, how often did you take your heart medications as your doctor prescribed?” scored from 1, “less than half of the time (< 50%),” to 5, “all of the time (100%)” (Cutter et al., 1991), and by using a 3-item scale psychometrically developed by Voils and colleagues (Voils et al., 2012). Aversive cognitions towards cardiovascular medications were assessed at 1 month by asking patients: “How often did” 1) “you miss your heart medication because you did not want to be reminded of your heart problem”, 2) “thinking about your heart medication make you feel nervous or anxious”, and 3) “thinking about your heart medication make you think about your

risk for future heart problems.” Patients responded using a five-point Likert scale scored from 1, “never,” to 5, “all of the time.” These items were based directly on the Enduring Somatic Threat theory framework (Edmondson, 2014).

Statistical approach.

To test whether suspected ACS-induced PTSD is associated with increased secondary risk at 1 year, we will use a Cox proportional hazards model with 1-month PTSD assessment ($PCL \geq 33$) predicting subsequent acute coronary heart disease event (non-fatal myocardial infarction or hospitalization for unstable angina) or all-cause mortality with adjustment for demographic and clinical variables, as well as depression ($PHQ \geq 10$) (Kroenke et al., 2009). The PCL cut point of 33 is used due to its being in the middle of the lower (30) and upper (35) bounds of the range of cut points suggested by the National Center for PTSD for a sample of civilians in a primary care setting or the general population, and was the estimated cutoff associated with increased recurrence risk in the 2013 meta-analysis. If there is a statistically significant association between suspected ACS-induced PTSD and secondary risk, we will determine whether medication nonadherence partially mediates the association between PTSD symptoms and MACE/ACM by running a mediation test with bootstrapping. Specifically, the predictor in this model will be PTSD symptoms assessed at the 1-month interview, the proposed mediator will be electronic adherence data measured prior to the 1-month interview, and the outcome will be occurrence of the secondary risk health events (described above) after the 1-month interview until the end of the study. As an exploratory aim, we will determine whether patients who “rule out” for ACS are at similarly increased risk of PTSD and adverse CVD outcomes in a sensitivity analysis limited to only those who rule out for ACS at baseline.

Sample size determination.

Sample for testing links among ED factors, PTSD, risk of mortality and recurrent MACE.

We expected that 8% to 10% of participants would have a cardiac event recurrence/ACM event during the year following their index cardiac event. In our previous study, 10.4% had a cardiac event recurrence/ACM in the year following their index cardiac event. The sample size calculations are based on the conservative estimate of 8% cardiac event recurrence/ACM and a 2-tailed test at $\alpha=0.05$. Although we anticipated higher retention rates, to provide conservative sample size estimates, we allowed for 15% of participants to be unavailable for follow-up at 1 year (although medical record data for the primary outcome will be available for almost all participants). Based on prior data, we anticipated that 10% to 15% of participants would have PTSD at the 1-month follow-up contact. Based on these estimates, we planned to enroll 1,741 participants, which we expect to yield a final sample size of 1,488 or larger. Of the 1,741, we expected that 1,567 would complete the 1-month assessment. For the association between PTSD incidence at 1 month and a new cardiovascular event/ACM in the 1 year after enrollment (hypothesis 1), the detectable hazard ratio is 2.39 assuming that the incidence of PTSD is 15% at 1 month.

Preliminary results

Table 1 shows the baseline characteristics of patients recruited to date. Participants are racially and ethnically diverse. They demonstrate a range of severity of their ACS conditions, medical comorbidities, prior PTSD symptoms, and depressive symptoms. Overall, the sample is characterized by a wide age range, an expected sex distribution, substantial racial/ethnic diversity, low socioeconomic status, and high medical and psychological comorbidity burden.

Discussion

Given that hundreds of thousands of patients present for ACS each year, it is imperative to determine the extent to which ACS is associated with the development of PTSD and the extent to which this medical event-induced form of PTSD—in addition to being psychologically debilitating in its own right—is associated prospectively with increased risk of CVD event recurrence and mortality. Then, as a next step, it is essential to examine the mechanisms by which ACS-induced PTSD contributes to secondary risk. One key mechanism may be nonadherence to secondary prevention medications.

The study design has several strengths. First, it benefits from assessing acute stress exposure at the critical time of the ED admission without causing additional, undue burden to patients or altering the course of care or medication habits. Second, it includes a large and diverse longitudinal cohort, which improves generalizability of findings to the larger population of NSTEMI/UA patients across the United States as well as to the even larger number of patients who present to the ED with ACS symptoms but are ruled out, particularly in racially and ethnically diverse, low-SES settings. Third, there is a high quality of measurement for all key variables, including the adjudication of ACS status by expert cardiologists, the objective measure of cardiovascular medication adherence, and attention to potential confounds (i.e., non-ACS-induced PTSD and depression at baseline). Fourth, the study is designed to identify factors that are most important to target for future interventions designed to offset the expected risk of cardiac recurrence, mortality, and PTSD in NSTEMI/UA patients.

The study has some limitations. Evidence of mediation does not definitively prove causality. That is, a causal pathway is not proven if their nonadherence mediates the association between PTSD symptoms and health outcomes. Nevertheless, the longitudinal design and attention to confounds (e.g., PTSD symptoms unrelated to the ACS event, ACS severity,

demographic characteristics) lends credence to a causal interpretation of findings. A second limitation is that the study's 12-month design precludes the possibility of following these same patients for longer periods after their potentially traumatic experience in the ED. Nevertheless, research suggests that ED factors do influence medical outcomes within 1 year (Pines et al., 2009; Shen & Hsia, 2011). A third limitation is that PTSD is assessed only by self-reported measures and not by psychiatric interview in this study. However, the PCL is the gold standard screening tool for PTSD, and yields a valid symptom severity index. Furthermore, if PCL symptoms predict increased cardiac risk, then there may be reason for physicians to use this easily administered measure during the course of clinical care for their ACS patients, irrespective of whether patients meet the diagnostic threshold for PTSD.

Conclusion.

This prospective observational study will be the most definitive study to date of PTSD as a psychological reaction to an acute cardiac event, and the short-term psychological outcomes and long-term cardiovascular outcomes associated with PTSD, including subsequent MI and death. It will also provide insight into the ED and hospital characteristics that may influence the development of PTSD after acute cardiovascular events. In providing an overview of our study design and methods, we hope to provide future investigators with a model of the assessment of psychological and secondary cardiovascular risk following ACS events in an acute setting. If our hypotheses are supported, we will have identified an important modifiable secondary risk factor (ACS-induced PTSD) that may be preventable through changes to the way patients are evaluated and treated in the ED and hospital. Although many ED factors are largely modifiable, no accepted guidelines exist for managing ED factors that can influence psychological outcomes. Further, these results may shed light on the pernicious problem of nonadherence to secondary

prevention cardiovascular medications, and point to novel psychologically-oriented interventions to improve adherence and secondary risk (as well as quality of life) in survivors of acute cardiovascular events.

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Table 1. Unless otherwise indicated, data are expressed as number (percentage) of patients.

Table 1

Demographic and clinical participant characteristics.

Demographic information	
Age, mean in years (SD)	60.54 (13.28)
Female	818 (47.0%)
Black	397 (24.0%)
Hispanic	1,003 (59.4%)
Education (completed high school)	1,137 (65.4%)
Current partner	751 (43.5%)
Current health insurance	1,537 (89.5%)
Medical information	
ACS confirmed: NSTEMI	311 (17.9%)
ACS confirmed: UA	230 (13.2%)
Prior cardiac event*	537 (30.8%)
Atherosclerotic disease	199 (11.7%)
GRACE score, mean (SD)	93.80 (29.98)
Charlson comorbidity index, mean (SD)	1.78 (1.98)
Psychiatric conditions at baseline	
Non-ACS-induced PTSD symptoms, mean (SD)	26.81 (13.71)
Baseline depressive symptoms, mean (SD)	6.61 (5.90)

*Record of prior confirmed myocardial infarction, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI)

Figure 1. Proposed theoretical model for investigating potential pathways connecting factors at the time of the initial emergency department (ED) visit in patients presenting with symptoms of acute coronary syndrome. ED factors in three domains predict subsequent post-traumatic stress disorder (PTSD), which predicts medical outcomes that may be partially mediated by changes in medication adherence.

Figure 2. Timetable for ReACH study procedures. The dotted vertical line indicates the transition between study phases occurring in the hospital versus at home. ED = emergency department. CVD = cardiovascular disease. ACS = acute coronary syndrome. ASD = acute stress disorder. PTSD = post-traumatic stress disorder.