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**CONCEPT SHEET: REGIONAL ANALYSES**

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| **Steering Group approval date:** | *(To be added by UCT data centre)* |
| **Tracking number:** | *(To be added by UCT data centre)* |
| **Title:** |  |
| **Lead author:**  **Email:** | Cristina Mesa Vieira (ISPM)  Cristina.mesavieira@ispm.unibe.ch |
| **IeDEA senior investigator:**  **Email:** | Andreas Haas (ISPM)  [andeas.haas@ispm.unibe.ch](mailto:andeas.haas@ispm.unibe.ch) |
| **Statisticians:**  **Email:** |  |
| **Data manager:**  **Email:** | Nicky Maxwell (IeDEA data centre at UCT)  nicky.maxwell@uct.ac.za |
| **Where will statistical analyses be done?** | ISPM, University of Bern |
| **Required variables:** |  |
| **Target journal:** |  |
| **Ethics:** | *Select as appropriate:*  This concept uses only the IeDEA-SA standard dataset and is covered by the core IeDEA-SA ethics approvals.  This concept requires additional collection of health-related data, measurements or tests, or sampling of biological material not included in the IeDEA-SA standard dataset. Additional ethics approval is required.\* (Describe ethical considerations for any additional data collection here, including responsible IRBs.) |
| **Milestones:** | *Circulation of concept sheet: April 1, 2022*  *Ethics approval (for additional data collection): <date>*  *Circulation of mature draft paper: <date>*  *Submission to target journal: <date>* |
| **Abstract:** (about 100 words) | **Background:**  **Aims and objectives:**  **Methods:** |

\* If additional ethics approvals are required, a copy must be sent to the ISPM Program Manager before data collection can begin.

**1. Background**

Posttraumatic stress disorder (PTSD) is a maladaptive reaction to a traumatic event, and it is present in about 7% of the population (1). The current scientific literature shows an association between PTSD and cardiovascular risk factors (2) and cardiovascular disease (CVD). For example, a recent systematic review (3) reported that persons with PTSD had a largely increased risk of subsequent myocardial infection (aHR 1.49, 95% CI 1.31-1.69).

Two pathways might explain the increased incidence of CVD in persons with PTSD. PTSD can lead to unhealthy behaviours such as substance use, physical inactivity, sleep disorders and dietary changes that lead to common cardiovascular risk factors (hypertension, diabetes, high cholesterol), which can cause CVD (2). An alternative explanation is that PTSD generates an inflammatory state that can cause CVDs such as myocardial infarction, unstable angina and stroke (2). This hypothesis is supported by studies showing that PTSD is independently associated with an increased risk of coronary heart disease even after adjusting for depression and cardiovascular risk factors, such as high cholesterol, hypertension and high blood pressure (ref).

The relationship between PTSD and CVD is bidirectional. Evidence suggests that a cardiovascular event can cause PTSD. For example, Edmonson found a 12% prevalence of PTSD secondary to acute coronary syndromes. PTSD, in turn, doubles the risk for recurrent acute coronary syndromes and mortality. The mechanisms through which CVD causally relates to PTSD are under study (2).

While evidence on the association between PTSD and CVD is emerging, there is little empirical support for causal links between PTSD and CVD. We aim to examine PTSD as a causal risk factor for CVD and quantify the mediating effect of PTSD on CVD through CVD risk factors.

**2. Objectives**

1. To describe the incidence of cardiovascular risk factors and major cardiovascular events in persons with and without PTSD
2. To examine PTSD as a causal risk factor for CVD (total effect)
3. To quantify the mediating effect of PTSD through CVD risk factor or inflammation on CVD (indirect effect via mediators).

**3. Study design**

We will conduct a cohort study of South African adults using routine data from a large South African medical insurance scheme.

**3.1 Eligibility criteria**

Adults aged 18 years or older who had insurance coverage with the medical insurance scheme at any point between January 1, 2011, and July 30, 2020, are eligible for analysis. Persons with unknown sex or age will be excluded.

**3.2 Key variables**

* Demographic data: age, sex, ethnicity
* Hospital admission data: International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes, National Reference Price List (NRPL) codes, Current Procedural Terminology (CPT) codes, date of admission, date of discharge
* Laboratory data
* Vital status
* Start and end of coverage, health care plan

**3.3. Assumptions**

The assumptions about the relationship between relevant variables are shown in a directed acyclic graph (DAG) (Figure 1). Ethnicity and associated socioeconomic disparities affect the risk of PTSD (ref) and depression (ref), and lifestyle factors (e.g. smoking, substance use, alcohol use, diet, and physical activity) (5). Lifestyle factors increase the incidence of cardiovascular risk factors (e.g. high blood pressure, obesity, high cholesterol, and diabetes) that in turn, may cause CVD (6).

ESH (ethnicity, socioeconomic status, type of health insurance) refers to baseline confounders that are related to the exposures (PTSD and depression) (4). However, there is also an array of mediators in between. ESH is associated to lifestyle (5), which in our model is presented as an unobserved variable, because of data availability. The evidence has shown that lifestyle (exercise, diet, sleep, smoking, medication non-adherence) leads to cardiovascular risk factors, such as high blood pressure, obesity, high cholesterol, that are causes of cardiovascular disease (6). As said earlier, both lifestyle and cardiovascular risk factors can cause PTSD (2), which is highly comorbid with depression. PTSD itself and through unhealthy behaviours (lifestyle) and inflammatory mechanisms (cardiovascular risk factors) can lead to cardiovascular disease (3). The evidence has shown that several types of cardiovascular events can be the underlying cause for PTSD (7), but we still need to establish whether this happens through the same two possible mechanisms (2).

**3.4 Definitions**

* For the exposure, we will classify diagnoses for PTSD (F43.1) and depression (F32.9) according to their ICD-10 codes.
* For the outcome, we classify the reason for admission as admission for cardiovascular event ICD-10 codes: myocardial infarction (I21), stroke (I63.9), unstable angina (I20).
* For the cardiovascular risk factors, we will use ICD-10 codes for diagnoses of hypertension (I10), obesity (E66), dyslipidaemia (E78.5), and diabetes mellitus (E11). These diagnoses will be confirmed with laboratory records.

**3.5 Data sources**

* We will use the Aid for AIDS (AfA) control database, which is a private-sector HIV treatment program that provides HIV care for patients on medical insurance and corporate treatment programs.29 AfA links laboratory, hospitalization, pharmacy and medical practitioner claims from the medical insurance fund claim database.
  1. **Statistical methods**

For this reason, we proposed the following directed acyclic graph to represent the assumptions based on what is already described in the literature.

*Descriptive analysis:* We will use descriptive statistics to analyse characteristics of participants with PTSD that belong to both private- and public-sector ART programs. Descriptive analysis will be stratified by sector (public/private) and history of cardiovascular disease treatment utilization (yes/no).

*Objective i:* We will calculate adjusted incidence rate ratios with 95% confidence intervals (CI), comparing the incidence of cardiovascular admissions between public- and private-sector ART programs using Poisson regression.31 Patients will be followed from PTSD diagnosis to their last documented clinic visit. We will model the number of hospital admissions recorded in patients with PTSD using Poisson regression). Models will be adjusted for current age, type of health insurance, gender and ethnicity and will use person-years at risk as an offset.

*Objective ii:* We will use causal inference to quantify the effect of PTSD on cardiovascular disease. The target quantity of interest in this analysis is the average treatment effect. The average treatment effect is defined as the expected outcomes under the counterfactual scenario where everyone was continuously affected by PTSD (always exposed) compared to the expected outcome under the scenario where nobody was affected (never exposed). Adjustment variables will be selected based on a direct acyclic graph (DAG) developed based on an extensive literature review and in consultation with domain experts. The target quantity will be estimated using longitudinal targeted maximum likelihood estimation (LTMLE). LTMLE is a state-of-the-art causal inference method for appropriate handling of time-depend exposures in the presence of time-dependent confounding affected by prior exposure. LTMLE reduces the chances of model miss-specification because it can incorporate flexible machine learning methods while retaining valid statistical inference.Risk of bias due to limitations of our data (e.g. unmeasured confounding) will be critically evaluated.

**3.7 Ethical considerations**

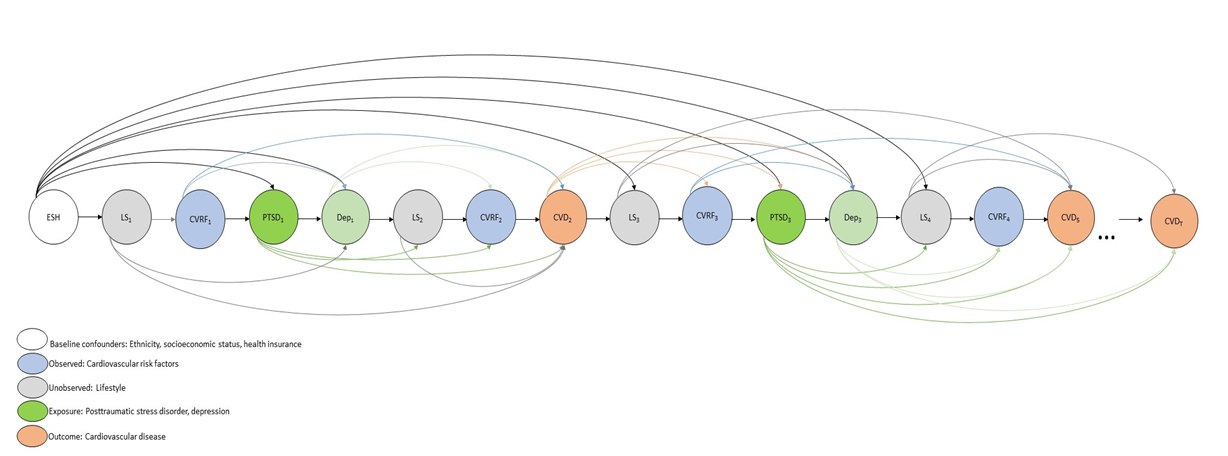
Data will be obtained from the AfA programme. All cohorts have IRB approval for contribution of their data to IeDEA for collaborative analyses. De-identified data will be sent to IeDEA data centre at Bern. The planned analyses will pose no risk or discomfort to individuals since it will not involve additional human subjects and will only use data that has been collected routinely.

Depression >>>> SU

https://www.sciencedirect.com/science/article/pii/S0149763416306996?via%3Dihub

“For example, comorbidity may manifest in individuals who use substances and their specific psychotropic effects to cope with [emotional distress](https://www.sciencedirect.com/topics/psychology/emotional-distress" \o "Learn more about emotional distress from ScienceDirect's AI-generated Topic Pages) and reduce dysphoric symptoms associated with depression ([Kessler, 2004](https://www.sciencedirect.com/science/article/pii/S0149763416306996?via%3Dihub" \l "bib0490), [Khantzian, 1985](https://www.sciencedirect.com/science/article/pii/S0149763416306996?via%3Dihub" \l "bib0495), [Khantzian, 1997](https://www.sciencedirect.com/science/article/pii/S0149763416306996?via%3Dihub" \l "bib0500), [Swendsen et al., 2010](https://www.sciencedirect.com/science/article/pii/S0149763416306996?via%3Dihub" \l "bib1030)) ([Fig. 1](https://www.sciencedirect.com/science/article/pii/S0149763416306996?via%3Dihub" \l "fig0005)a).”

We are not considering the effect of SU >>>>> Depression



**4. References**

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