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Characterizing the Trajectory of Depression and Associated Risk Factors Following an ABI in Adults: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 November 2023 and was last updated on 03 November 2023.

INTRODUCTION

Review question / Objective This review will aim to understand the different trajectories of depression in adults following an acquired brain injury (ABI) through a systematic review and possibly a meta-analysis. Specifically, the review will focus on the following objectives: (1) to characterize the distinct longitudinal patterns of change in the severity of depressive symptoms following an ABI and (2) to identify whether risk factors such as age, sex, level of education, premorbid psychiatric history, and injury severity are associated with specific depression trajectories.

Rationale Depression often persists in individuals with ABI, with individuals experiencing depressive symptoms for up to a decade post-injury (Grauwmeijer et al., 2018). A systematic review conducted by Scholten et al. (2016) revealed that 17% of individuals had depression in the first year after a brain injury, and this rate escalated to 43% over time. This persistent depression significantly affects daily functioning leading to decreased quality of life and increased dependency on others for activities of daily living (Juengst et al., 2015; Ponsford et al., 2014).

Longitudinal studies provide a range of findings regarding the trajectory of depression following a brain injury. Some studies report increased depressive symptoms (Gould et al., 2011), while others show stability (Hart et al., 2012), and some even reveal improvements in symptoms (Rapoport, 2012). Hence, there is no consensus on the trajectory of depression over time. However, many statistical techniques employed in longitudinal studies assume that the entire population follows the same depression trajectory, which disregards the heterogeneity within the ABI population. Consequently, this provides an inaccurate estimate of change over time (Ren et al., 2017). Group-based trajectory modelling (GBTM) is a valuable statistical technique for addressing this heterogeneity. GBTM identifies distinct classes of individuals within the population, each following unique trajectories over time. Instead of modelling the entire population's trajectory, GBTM estimates

trajectory parameters for each group. This approach allows for a more accurate and nuanced understanding of the course of depression post-ABI (Nagin & Odgers, 2010).

Research has identified distinct depression trajectories following a brain injury, including resilience (a subgroup of individuals who display improvements in depressive symptoms over time), stable low depression, persistently high depression, and delayed depression (a subgroup of individuals who develop depressive symptoms over time) (Ayis et al., 2019; Bombardier et al., 2016; Carmichael et al., 2023; Gomez et al., 2017; Ren et al., 2017). However, outcomes vary with some individuals displaying ongoing resilient traits while others exhibit persistent depressive symptoms (Ren et al., 2017; Sigurdardottir et al., 2014). Moreover, groups characterized by delayed and severe symptoms of depression have shown substantial fluctuations in depression levels over time, occasionally falling below clinically significant thresholds (Gomez et al., 2017).

Understanding the risk factors associated with specific depression trajectories can shed light on why particular individuals display persistent depression while others do not. For instance, research has shown that women with brain injuries tend to have more significant and persistent depression compared to men (Ayis et al., 2019; Gomez et al., 2017). Additionally, middle-aged individuals are more likely to belong to the persistent depression group which could be due to significant disruptions in daily life roles (Bombardier et al., 2016; Carmichael et al., 2023). While some studies have indicated a correlation between severe brain injuries and persistent depressive symptoms (Bombardier et al., 2016; Gomez et al., 2017; Ren et al., 2017), contrasting findings have shown that individuals with more severe brain injuries were part of the resilience group (Sigurdardottir et al., 2014).

To date, the trajectory of depression after ABI remains poorly characterized. Existing literature consists of numerous individual studies, each employing varying methodologies, sample sizes, and findings. Employing a systematic review and meta-analysis can consolidate this knowledge to offer a more comprehensive view of depression trajectories following brain injury (Scholten et al., 2016). Consequently, this review aims to (1) characterize the longitudinal patterns of change in depressive symptoms following an ABI and (2) identify the risk factors that are associated with specific depression trajectories. This knowledge is crucial for estimating prognosis and informing early intervention strategies tailored to meet the unique needs of each individual.

Condition being studied This review aims to comprehensively explore the natural course of depression in adults with ABI. Acquired brain injury (ABI) refers to damage to the brain after birth, excluding congenital and degenerative conditions (Rees et al., 2007) and is a leading cause of disability and activity limitation (AIHW, 2004). The prevalence of ABI is steadily growing in the adult population (Andelic et al., 2018), with accidents, stroke, and hypoxia being common causes (AIHW, 2004). Most ABIs are heterogenous with mechanisms of focal and diffuse injuries occurring in a single brain injury (McKee & Daneshvar, 2015; Skandsen et al., 2010). These injuries can disrupt specific brain areas and the communication between brain regions (Skandsen et al., 2010). As a result, ABI is associated with a cascade of sequala including cognitive deficits, movement impairments, and psychiatric disorders (Andelic et al., 2016). These repercussions can translate into long-term functional impairments, hindering the individual's ability to return to their normal life (Juengst et al., 2015; Ponsford et al., 2014).

Depression is characterized by persistent feelings of sadness, hopelessness, and loss of interest in previously enjoyed activities and affects more than half of individuals with brain injuries (American Psychiatric Association, 2013; Fann et al., 2009; Musliner et al., 2016). The understanding of underlying pathophysiological mechanisms of depression in individuals with brain injury is limited due to the heterogenous nature of the injury. Several proposed mechanisms contribute to depression following a brain injury, including changes in inflammatory pathways (Bodnar et al., 2018), neurotransmitter dysfunction (Prins et al., 2013), and mitochondrial damage (Czarny et al., 2018). Moreover, studies have shown that white matter abnormalities and network disruptions in brain regions such as the frontal and temporal cortex have been significantly associated with depression (Griffis et al., 2019; Smith et al., 2019; Tham et al., 2011). Additionally, adjustment and adaptation to life following a brain injury can influence depressive symptoms (Rogers & Read, 2007). For example, an individual's ability to assess their capabilities following a brain injury compared to their abilities pre-injury has been reported as an underlying factor related to the development of psychiatric disorders such as depression (Draper & Ponsford, 2009; Ponsford et al., 2013). These individuals often face difficulties in engaging in goal-directed tasks and problem-solving behavior which contributes to increased depressive symptoms (Levine et al., 2011). Depression can manifest as difficulties in daily activities, returning to work and in relationships, thus decreasing the

quality of life for the affected individual (Ponsford et al., 2014).

METHODS

Search strategy The review will align to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An extensive literature search will be conducted using the following online databases: MEDLINE, PSYCHINFO, ScienceDirect, Scopus, EMBASE, CINHAL and Web of Science. Grey literature search will be conducted using the following databases: ProQuest Dissertations & Theses Global, Open Grey, Grey Net International and Grey Matters. Studies will be included that assess depression over three or more time points in an ABI sample and use GBTM. Searches will be re-run prior to the final analyses and any additional identified studies will be included.
Concept 1: (head OR brain OR crani* OR cerebr*) ADJ2 (injur* OR incident* OR trauma* OR damage* OR accident*) OR (brain-ischemi*) OR stroke* OR (diffuse-axonal-injur*) OR TBI OR ABD OR ABI
Concept 2: depress* OR MDD OR (major-depressive-disorder) OR (depressive-disorder) OR (major-depression) OR (psychological-distress)
Concept 3: ((group-based-trajectory-model*) OR (growth-mixture-model*) OR (latent-growth-curve-model*) OR (latent-class-growth-analys*).

Participant or population This review will only include studies with an adult population (16 – 70 years old) with an ABI. ABI is comprised of traumatic brain injury (TBI) and non-TBI including aneurysm, stroke, brain tumor and hypoxia. Full inclusion and exclusion criteria are listed below.

Intervention Not applicable.

Comparator As most longitudinal studies focusing on depression within the brain injury population predominately employ a within-subjects design, this review will not include a comparator group. Comparative intervention studies will not be within the scope of this review, as our primary objective will be looking at the natural progression of depression trajectory after a brain injury.

Study designs to be included This review will include studies that assess depression at a minimum of three or more time points. Therefore, the review will include longitudinal and prospective studies. Studies will be excluded that are case studies, animal studies, and cross-sectional studies.

Eligibility criteria The inclusion criteria for the studies selected will be limited to a) studies published in English language, b) peer-reviewed studies with full-text available, c) studies that use an adult population (16-70 years old), d) inclusion of ABI diagnosis with acute onset of injury for participants, e) an independent measure of depression, or a depression scale incorporated within a broader assessment tool, f) studies have a minimum of three assessment time points, and g) studies that employ a type of GBTM. Hand searching will be conducted to supplement electronic searches and unpublished studies will be pursued. Studies will be excluded if a) the sample includes participants with neurodegenerative diseases (e.g. dementia) or neurodevelopmental disorders, b) the study solely focuses on treatment or intervention and c) have samples with specific neurological conditions.

Information sources Peer-reviewed articles will be searched on online databases: MEDLINE, PSYCHINFO, ScienceDirect, Scopus, EMBASE, CINHAL and Web of Science. Studies will also be hand-searched. Grey literature search will be conducted using the following databases: ProQuest Dissertations & Theses Global, Open Grey, Grey Net International and Grey Matters.

Main outcome(s) Depression trajectory measured by validated depression self-report measure over three or more time points.

Additional outcome(s) Sample age, sex, education, premorbid psychiatric history, injury severity and time since injury.

Data management The author will screen various databases for studies that can be included in the review. All stages of data screening and extraction will be managed using Covidence software. Once duplicates are removed the lead author will screen titles and abstracts against the outlined inclusion and exclusion criteria. Full text screening will occur for the remaining articles. A second author will impartially screen 30% of the articles for inclusion in the review at each stage of the screening process. Exclusion reasons will be recorded and the level of agreement between two authors. The research team will assess decisions and any disagreements regarding judgements will be resolved. Papers will be assessed for inclusion using the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) critical appraisal criteria.
The data will be manually obtained by the lead author and checked by a second author. Authors will be contacted to obtain missing data or clarify

any uncertainties. All extracted data will be recorded using Excel. Extracted data will include:
• Study title, author, journal, location, and year of publication
• Aim of study
• Study funding sources and reported conflicts of interest
• Participant recruitment method and setting
• Sample demographics include age, sex compositions, educational history, premorbid psychiatric history
• Brain injury characteristics, including injury type, severity and time since injury
• Measures of depression used in the study
• Statistical modelling technique
• Number of trajectory groups
• Number of time points measured
• Average depression scores at each time point.

Quality assessment / Risk of bias analysis The quality of the finale selected studies will be examined according to the Joanna Briggs Institute Critical Appraisal Tools (Aromataris et al., 2015).

Strategy of data synthesis The review will present a comprehensive qualitative synthesis of its findings. Sample characteristics, depression scores, and injury characteristics will be summarized. The systematic review will shed light on the most common depression trajectories following a brain injury, elucidating the shape, pattern, and prevalence of each distinct trajectory group. Furthermore, the review will examine factors that are associated with membership in specific depression trajectories.
If sufficient data on depression scores and depressive symptom cut-off scores are available from all selected studies, a meta-analytic review will be conducted. To ensure consistent trajectory estimates, depressive symptom scores will be recalibrated across all selected studies to align with the most used depression measure. As of the current preliminary search process, the most commonly used measure identified is the Hospital Anxiety and Depression Scale (HADS). The review will redefine depression trajectory labels to match the HADS item measures based on symptom cut-offs. This categorization will classify them into three distinct levels of depression: 'Low' (scores ranging from 0 to 10), 'Moderate' (scores ranging from 11 to 15) and 'High' (scores ranging from 16 to 21). A random-effects meta-analysis will be conducted using the packages 'metafor' and 'escalc' in RStudio. This analysis will explore the prevalence of depression trajectory groups that fall above and below the clinical cut-off threshold, and the prevalence different trajectory patterns, such as those with increasing or decreasing depressive symptoms. To account for potential variations across studies, sensitivity analyses and random-effects model will be employed. Furthermore, a systematic review will be conducted to identify and analyze risk factors associated with each trajectory group.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Language restriction English Language only.

Country(ies) involved Australia.

Keywords acquired brain injury, depression, group-based trajectory modelling, risk factors, systematic review, meta-analysis, neuropsychology.

Dissemination plans The author will aim to publish the results in a peer-reviewed journal article.

Contributions of each author
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