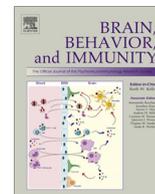




Contents lists available at ScienceDirect

## Brain, Behavior, and Immunity

journal homepage: [www.elsevier.com/locate/ybrbi](http://www.elsevier.com/locate/ybrbi)

## Characterising acute coronary syndrome-associated depression: Let the data speak

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### ARTICLE INFO

#### Article history:

Received 18 December 2014  
Received in revised form 24 February 2015  
Accepted 2 March 2015  
Available online xxx

#### Keywords:

Acute coronary syndrome  
Depression  
Biological profiling  
Inflammation  
Heart rate variability

### ABSTRACT

Depression in the context of acute coronary syndrome (ACS) is understood to confer increased morbidity and mortality risk. The pathophysiological mechanisms underlying this association remain poorly understood, although several candidates including inflammation, cardiac autonomic dysregulation, and behavioural factors are viewed as of key importance. No single bio-behavioural explanatory model of ACS-associated depression has emerged, likely due the substantial heterogeneity across both conditions. We studied 344 patients with ACS; 45 fulfilled diagnostic (DSM-IV) criteria for a major depressive episode occurring within 1-month of ACS, and 13 had ongoing major depression that pre-dated ACS and continued through to 1 month post-ACS. We employed two statistical methods (multinomial logistic regression; and latent class analysis) and a range of immunological, autonomic and nutritional markers in an attempt to characterise a biological basis for ACS-associated depression. Regression modelling failed to accurately predict categorical group membership of ACS-associated depression. An alternative data-driven approach produced a three-class solution, with the derived classes differing on measure of C-reactive protein, vitamin D, omega-6:omega-3 ratio, heart rate variability, and age (all  $p \leq 0.004$ ). The majority of participants with ACS-associated and ongoing depression were members of the class characterised by the greatest biological disturbance. Patients with depression differed from those without depression on a range of psychological trait and state variables; additionally reporting poorer sleep quality, higher levels of social isolation, and functional impairment, but had similar biological profiles. Patients with ongoing depression generally had higher scores on these psychological/behavioural measures. Our novel analytic approach identified a combination of biomarkers suggestive of a role for immune, autonomic, and nutritional pathways in the manifestation of depression during ACS, in the context of additional psychosocial and behavioural vulnerabilities. Further studies are required to confirm the causal role of these factors in perpetuating depression and increasing risk of poor-health outcomes.

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### 1. Introduction

Patients with heart disease are around four times more likely to develop depression than the general population (Freedland and Carney, 2013; Nemeroff and Goldschmidt-Clermont, 2012). In those with acute coronary syndrome [ACS; myocardial infarction or unstable angina], comorbid depression is increasingly recognised as an independent risk factor for adverse medical outcomes including mortality (Celano and Huffman, 2011; Lichtman et al., 2014; Meijer et al., 2011). These observations have led some researchers to propose that ACS-associated depression may be qualitatively different from that seen in psychiatric samples; yet

research exploring a possible biological basis for depression in the context of ACS has so far produced inconclusive evidence (Drago et al., 2007; Frasure-Smith et al., 2009; Holt et al., 2013; Parker et al., 2008; Shimbo et al., 2006; Steptoe et al., 2013). As the diagnostic labels 'ACS' and 'depression' each encompass a broad and heterogeneous group of individuals (Carney and Freedland, 2012; Davidson, 2012), it is not surprising that a simple explanatory model has not emerged. However, complex analyses that allow exploration of the contributions of several biological systems are not often attempted.

While the biological underpinnings of ACS-associated depression remain obscure, several candidates are considered of key importance; notably a role for inflammation, as well as cardiac autonomic regulation, is widely recognised. A significant rise in inflammatory proteins in the wake of ACS are thought to trigger the development of depression and predispose towards poor prognosis (He et al., 2010; Kaptoge et al., 2010; Poole et al., 2011;

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Shaffer et al., 2011). However, a recent report of cytokine production in the local coronary micro-environment revealed that patients with ACS differ substantially in regard to activation of inflammatory pathways, with only half showing a striking increase in cytokine production (Cirillo et al., 2014). Furthermore, increased levels of inflammatory markers preceded the development of depression in approximately only one third of individuals when exposed to the same immunogenic stressor (Raison and Miller, 2011; White et al., 2001). Autonomic nervous system (ANS) dysfunction, as indexed by low heart rate variability (HRV) has additionally been proposed a candidate mechanism linked to both ACS and depression (Harris et al., 2014a; Stapelberg et al., 2012; Taylor, 2010; Thayer and Lane, 2007). In those with comorbidity, low HRV has been shown to predict further cardiac events and mortality (Carney et al., 2005; Harris et al., 2014b; Hillebrand et al., 2013; Kop et al., 2010; Taylor, 2010; Thayer and Lane, 2007).

The impact of health behaviours on cardiovascular morbidity and mortality is widely recognised, with restorative sleep, balanced nutrition, and adequate exercise considered of key importance (Blumenthal et al., 2005; Chrysohoou et al., 2011; Laugsand et al., 2011). A growing body of evidence documents that the health effects of sleep are mediated via its impact on multiple biological pathways affecting inflammatory, neuroendocrine, autonomic, and metabolic regulation (Alcántara et al., 2014; Faraut et al., 2012; Grandner et al., 2013; Irwin, 2015; Opp, 2005; Yoshino and Matsuoka, 2009). Poor sleep has been linked to an increased risk of developing heart disease (Spiegelhalter et al., 2010) and may contribute to ACS pathogenesis (Bonnet and Arand, 2007; Fernandez-Mendoza and Vgontzas, 2013; Grandner et al., 2013; Mullington et al., 2009). Insufficient sleep following ACS has also been associated to recurrence of cardiac events and mortality (Alcántara et al., 2014). Additionally, poor sleep is recognised to constitute both a predisposing factor and a symptom of depression (Adrien, 2002; Baglioni et al., 2011; Irwin, 2015; Lee et al., 2013; Tsuno et al., 2005).

The purported health benefits of specific nutrients have been studied in the context of ACS-associated depression. Polyunsaturated fatty acid (PUFA) omega-3 (n-3) levels have been linked to both ACS and depression, with reported beneficial effects on inflammation, HRV, cardiovascular health, as well as mood (Appleton et al., 2010; Bloch and Hannestad, 2012; Calder, 2012; Lin and Su, 2007; Mozaffarian and Wu, 2011; Patterson et al., 2012; Riediger et al., 2009). Below average levels of n-3 have been reported in patients with ACS and depression (Frasure-Smith et al., 2004; Parker et al., 2006b). The health benefits of vitamin D have recently attracted attention, with deficiency in serum 25-hydroxyvitamin D (25[OH]D; vitamin D) levels linked to an increased risk of cardiovascular events (Artaza et al., 2009; Lee et al., 2008; Wang et al., 2008). Low levels of vitamin D have also been associated with depression (Berk et al., 2007; Hoang et al., 2011). Support for relationships between nutritional status and health outcomes are far from unanimous; recently an inconclusive review of the efficacy of vitamin D and n-3 PUFA for heart disease highlighted an absence of an appropriate general dose for both supplements (Güttler et al., 2012). Nonetheless, assessing PUFA and vitamin D levels at the time of ACS and their relationship to other biomarkers may contribute to defining better biological profiles linked to the risk of developing ACS-associated depression.

Current research exploring biological mechanisms underlying ACS-associated depression has mostly focussed on specific biological hypotheses, notably immune activation (Shimbo et al., 2006; Steptoe et al., 2013). The possible combined effect of several biological pathways on depression in the context of ACS has not been evaluated in any depth. Moreover, studies to date appear to have searched for a biological explanation in patients with ACS-associated depression as a unified group using top-down methods.

Such an approach presumes that a single explanatory model can be defined which, given the heterogeneity of the conditions in question, seems unlikely.

Our study is unique in its inclusion of a broad array of biological variables (including inflammatory, autonomic, nutritional, and sleep variables) as potential predictors of ACS-associated depression. Further, we undertook two different statistical approaches in an attempt to characterise a biological profile underpinning ACS-associated depression. In the first instance, we utilised a combination of biomarkers and multinomial logistic regression modelling to test if we could predict categorical membership of ACS-associated depression. We found that this top-down method failed to characterise a biological profile predictive of ACS-associated depression. A second data-driven approach used these biological variables to derive a multi-class model, in which participants are assigned to classes on a probabilistic basis. The occurrence of depression within each of these classes, as well as the variables differentiating depressed from non-depressed participants within classes, were then explored.

## 2. Methods

### 2.1. Study design

Participants were consecutively recruited from patients admitted with ACS to cardiology wards at Prince of Wales Hospital (Sydney, Australia) between June 2010 and November 2013. Initial assessment took place on average 4.5 days ( $\pm 4.2$  days; median = 3 days) after the participants' acute cardiac event. Information regarding cardiac disease severity (i.e., left ventricle ejection fraction [LVEF], peak troponin T levels, recent invasive surgery), medical diagnoses and history were obtained via medical records. At initial assessment, a clinical interview and questionnaires were used to obtain information regarding demographics, depression status, psychosocial and health/lifestyle factors. Additionally, a blood sample was provided and participants undertook tests of autonomic functioning. Follow-up interviews to monitor participants' mental and physical health were conducted over the telephone at 1-month after initial assessment.

### 2.2. Participants

Three hundred and forty four patients with confirmed ACS were recruited; all fulfilled the additional inclusion criteria of: 18 years or older, no visual or hearing impairment, able to speak and understand English, no concurrent infection, and no elevated mortality risk from comorbid conditions. The study protocol was approved by the relevant institutional human research ethics committee. Written consent was obtained from all who agreed to participate.

### 2.3. Assessments

#### 2.3.1. Clinical interview

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a current major depressive episode (MDE) and a lifetime history of depression were assessed via structured clinical interview using the MINI – International Neuropsychiatric Interview (version 6.0; Sheehan et al., 1998). The MINI was administered as part of the initial assessment, and repeated during the 1-month follow-up to confirm the required period of continuous depression. A positive diagnosis of a MDE required participants to endorse experiencing at least five of nine key symptoms (e.g., significant changes in appetite, psychomotor slowing, difficulties concentrating, etc.) for a period of at least 2 weeks; at least one of which was continuously feeling depressed, or experiencing a loss of interest or pleasure.

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