

## Research paper

# Trait anxiety mediates the effect of stress exposure on post-traumatic stress disorder and depression risk in cardiac surgery patients



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## ABSTRACT

**Background:** Post-traumatic stress disorder (PTSD) and depression are common after cardiac surgery. Lifetime stress exposure and personality traits may influence the development of these psychiatric conditions.

**Methods:** Self-reported rates of PTSD and depression and potential determinants (i.e., trait anxiety and stress exposure) were established 1.5 to 4 years after cardiac surgery. Data was available for 1125 out of 1244 (90.4%) participants. Multivariable linear regressions were conducted to investigate mediating and/or moderating effects of trait anxiety on the relationship between stress exposure, and PTSD and depression. Pre-planned subgroup analyses were performed for both sexes.

**Results:** PTSD and depression symptoms were present in 10.2% and 13.1% of the participants, respectively. Trait anxiety was a full mediator of the association between stress exposure and depression in both the total cohort and female and male subgroups. Moreover, trait anxiety partially mediated the relationship between stress exposure and PTSD in the full cohort and the male subgroup, whereas trait anxiety fully mediated this relationship in female patients. Trait anxiety did not play a moderating role in the total patient sample, nor after stratification on gender.

**Limitations:** The unequal distribution of male (78%) and female patients (22%) might limit the generalizability of our findings. Furthermore, risk factors were investigated retrospectively and with variable follow-up time.

**Conclusions:** In cardiac surgery patients, trait anxiety was found to be an important mediator of post-operative PTSD and depression. Prospective research is necessary to verify whether these factors are reliable screening measures of individuals' vulnerability for psychopathology development after cardiac surgery.

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## 1. Introduction

Patients undergoing cardiac surgery are at high risk of developing post-traumatic stress disorder (PTSD) and depression. These problems occur in up to 15% and 20% of the patients, respectively (Griffiths et al., 2007; Tully, 2012), and may hamper full recovery (Granja et al., 2012; McKhann et al., 1997; Pirraglia et al., 1999).

Stress exposure during life may alter hypothalamic-pituitary-adrenal (HPA) axis responses when encountering novel stressful

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situations (Binder et al., 2008; Maripuu et al., 2014). Furthermore, stress exposure during childhood has long-term consequences on the ability to cope with stressors later in life (Horovitz et al., 2012). The influence of lifetime stress exposure on the development of psychopathology (i.e., PTSD and depression) in cardiac surgery patients is currently unknown.

The impact of lifetime stress on an individual depends partially on personality traits, such as anxiety (DiGangi et al., 2013; Kadak et al., 2013; Spielberger et al., 1983; van der Ploeg, 1980; van Reedt Dortland et al., 2012; Vinkers et al., 2014). High trait anxiety is common among cardiac patients and associated with core symptoms of PTSD (Jakšić et al., 2012; Jones et al., 2001; Kress et al., 2003). We hypothesized that the relation between lifetime stress exposure and psychopathology is mediated or moderated by the individual variation in trait anxiety. Identifying a mediating effect would imply trait anxiety to be a key factor in the causal pathway of lifetime stress exposure to psychopathology, and thus potentially amenable for interventions. A moderating role of trait anxiety would provide a more precise estimate of individual vulnerability to psychopathology after lifetime stress exposure and thereby contribute to our understanding of disease etiology (Kraemer et al., 2008).

The aim of this study was to investigate the mediating and/or moderating effect of trait anxiety on the relationship between childhood trauma and stressful life events on the one hand, and the post-operative development of PTSD and depression in cardiac surgery patients on the other hand.

## 2. Materials and methods

### 2.1. Patients

Patients of 18 years and older who were scheduled for cardiac surgery requiring cardiopulmonary bypass were eligible to participate in the Dexamethasone for Cardiac Surgery (DECS) study (Clinicaltrials.gov identifier: NCT00293592). DECS study participants were randomized to receive dexamethasone or placebo (1 mg/kg bodyweight) intravenously during surgery in a double-blind way. Details of the study design have been published

previously (Dieleman et al., 2012). For the present study, patients who participated in the DECS study a maximum of 3.5 years ago were recruited from the five cardiac surgery centers which yielded approximately 90% of the original DECS study sample: University Medical Center Utrecht, Isala Clinics, Amphia Hospital, University Medical Center Groningen, and Erasmus Medical Center. Participants ( $n=2458$ ) were assessed for eligibility between April 2006 and November 2011. Exclusion criteria were derived from the DECS study, and encompassed a life expectancy of 6 months or less, or an off-pump cardiac surgery procedure. There were no additional exclusion criteria for the present follow-up study. Time between cardiac surgery and the current assessment of lifetime and present psychopathology and postoperative psychopathology varied from 1.5 to 4 years.

### 2.2. Data collection

Participants received questionnaires by mail and a reminder by telephone, in order to increase the response rate. After obtaining written informed consent for the current study ( $n=1244$ ; 50.6% of the eligible participants of the DECS study sample), 1125 (90.4%) patients returned questionnaires (Fig. 1). All questionnaires were scanned at once, and correspondence of digitized scores with the paper questionnaires was checked (in 5% of randomly selected participants). The Medical Ethics Committee of the University Medical Center Utrecht approved this study.

### 2.3. PTSD and depression

Symptoms related to PTSD were measured by the Self-Report Inventory for PTSD (SRIP), which was previously well validated (van Zuiden et al., 2011, 2012) though not specifically after ICU treatment. The SRIP is a 22 item questionnaire which addresses DSM-IV-TR criteria of PTSD in the past four weeks (Hovens et al., 2000). It is rated on a 4-point (0–3) Likert scale, with higher scores indicating the presence of more symptoms. A literature-based cut-off score of 39 (sensitivity=0.74, specificity=0.81) was used to detect if above threshold symptoms of PTSD (for clarity, further referred to as PTSD) were present (van Zelst et al., 2003a; 2003b). Internal consistency is good with Cronbach's alpha scores ranging

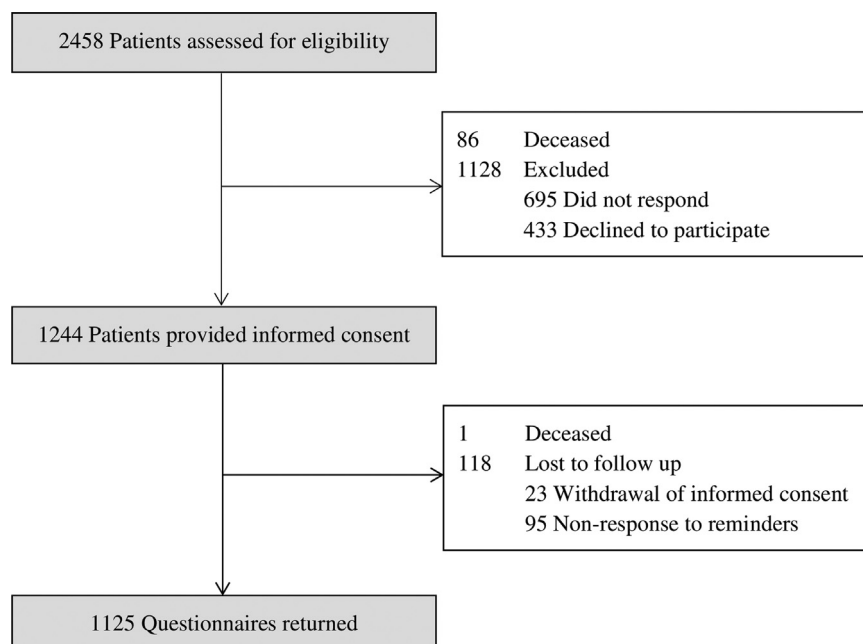


Fig. 1. Flow chart.

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