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Research paper

Stress-related psychopathology after cardiac surgery and intensive care treatment

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ABSTRACT

Objective: Cardiac surgery patients are at risk for psychopathology. Symptoms of post-traumatic stress disorder (PTSD) and depression occur in 10–20% of these patients and affect their quality of life. The aim of this study was to assess factors associated with psychopathology after cardiac surgery.
Methods: We followed participants of the multi-center randomized clinical trial Dexamethasone for Cardiac Surgery (DECS), on a single, intravenous dose of dexamethasone (1 mg/kg) or placebo during cardiac surgery, using validated questionnaires to assess PTSD and depressive symptoms after 1.5 to 4 years, as well as childhood trauma, trait anxiety, pre-existing psychopathology, and substance use. Saliva was used for genotyping of the hypothalamic-pituitary-adrenal-axis (HPA axis) glucocorticoid receptor gene. Linear backward regression analysis was performed with these factors, including pre-specified interaction terms of dexamethasone with sex and genotype.
Results: Complete data was available for 90% of cases (n = 1111). The model including trait anxiety and the [dexamethasone x female sex] interaction explained 57% of variance in PTSD symptoms (Model fit F (2;4.817)= 643.043, p<.001; R^2=0 0.57). Similar explained variance was seen for depressive symptoms, where age, trait anxiety and the [dexamethasone x female sex] interaction provided the optimal model (Model fit F (3;4.261)= 435,960, p<.001; R^2=0.58).
Limitations: In this study psychopathology was assessed through validated questionnaires. Variability in data collection detail was present.
Conclusion: This study suggests that the occurrence of psychopathology after cardiac surgery is influenced by higher trait anxiety. Female cardiac surgery patients may benefit from intra-operative dexamethasone administration.

1. Introduction

The beneficial effects of cardiac surgery and subsequent intensive care unit (ICU) treatment can be hindered by the development of psychopathology after hospital discharge. In the first year after surgery, post-traumatic stress disorder (PTSD) and depression occur in 10% to 20% of the patients (Schelling et al., 2003). In a previous study concerning cardiac surgery patients, we found symptoms of post-traumatic

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stress disorder (PTSD) and depression to occur in 10.5% and 13.1% of patients, respectively (Kok et al., 2016a). These complications can be invalidating, and interfere with successful recovery (Schelling et al., 2003; Stoll et al., 2000; Tedstone and Tarrier, 2003; Hauer et al., 2011; Yehuda, 2000; Yehuda et al., 2004). It is therefore important to identify factors that may affect the development of psychopathology after cardiac surgery and ICU stay, to facilitate early treatment of patients at risk (Spijker and van Rossum, 2012; Gibbison et al., 2015). However, which factors contribute most to psychopathology and may guide potential interventions, is currently unclear.

Substance use and prior psychiatric conditions are known determinants for recurrent psychopathology (Lewinsohn et al., 2000; Spertus et al., 2003). Also, childhood trauma – in particular emotional neglect – is thought to influence the response to novel stressful situations, and thereby the development of stress-related psychopathology (Klein et al., 1999). Recently, we showed that intraoperative dexamethasone administration can reduce PTSD symptoms in female cardiac surgery patients (Kok et al., 2016a). This effect was dependent on specific genetic variations of the target receptor of dexamethasone, the glucocorticoid receptor (GR). A comparable relation with dexamethasone – although not statistically significant – was found with regard to symptoms of depression. Importantly, high trait anxiety also plays a role; this common personality trait mediates the effect of stress-exposure prior to cardiac surgery on the development of symptoms of PTSD and, to a lesser extent, depression thereafter (Kok et al., 2016b). These findings indicate that pre-operative screening of cardiac surgery patients, based on the afore-mentioned factors, might be informative of individual vulnerability to develop psychopathology.

The aim of this study was to identify among those factors that were earlier investigated, those that explain most of the variation of symptoms of PTSD and depression after cardiac surgery and subsequent ICU stay, which is relevant on a population level. We studied patient related factors (i.e., advanced age, female sex, history of psychopathology, substance use, emotional neglect during childhood), personality traits (i.e., trait anxiety), medication that affects the hypothalamic-pituitary-adrenal (HPA) axis (i.e., dexamethasone), and genetic factors (i.e., polymorphisms of the glucocorticoid receptor gene).

2. Materials and methods

2.1. Study design and patients

Between April 2006 and November 2011, 4494 patients were randomized in the double-blind Dexamethasone for Cardiac Surgery (DECS) trial (Clinicaltrials.gov identifier NCT00293592). All included patients were 18 years or over and electively underwent cardiac surgery requiring cardiopulmonary bypass. A single dose of dexamethasone (1 mg/kg bodyweight, with a maximum of 100 mg) or placebo was administered intravenously after induction of anesthesia, and before starting cardiopulmonary bypass. This trial aimed primarily to quantify the effect of dexamethasone on the incidence of major adverse events in patients undergoing cardiac surgery. A further detailed trial design was described previously (Dieleman et al., 2012).

Between December 2012 and July 2013, 2458 patients who were included in the DECS trial were invited to participate in the present follow-up study on psychopathology, 1.5 to 4 years after their randomization (Kok et al., 2016a). These patients underwent cardiac surgery at the University Medical Center Utrecht, Isala Clinics, Amphia Hospital, University Medical Center Groningen, and Erasmus Medical Center. Additional written informed consent was obtained in 1244 patients (27.7% of the original DECS study sample). They received questionnaires and Salivettes by mail to obtain data regarding stress-related psychopathology, additional baseline characteristics (see below) as well as treatment and genetic information. Non-responders received reminders by telephone. All returned questionnaires were digitalized, after which correspondence with paper questionnaires was checked in 5% of randomly selected participants.

2.2. Outcomes: symptoms of post-traumatic stress disorder and depression

The Self-Rating Inventory for PTSD (SRIP) was used to assess presence of PTSD symptoms in the past 4 weeks (Hovens et al., 2000). This 22-item Dutch questionnaire is well-validated and evaluates PTSD in adults in correspondence with the Diagnostic and Statistical Manual of Mental disorders, 4th Edition (DSM-IV-TR) criteria for PTSD (Hovens et al., 2000). A possible maximum score of 88 is yielded by rating items on a 4-point (0–3) Likert scale; higher scores represent more severe PTSD symptoms. A total score of 39 was used as a cutoff value (sensitivity=0.74, specificity=0.81), indicating above threshold symptoms of PTSD. This questionnaire is validated in different populations, and attains a high internal reliability with Cronbach's alpha ranging between 0.90 and 0.94 for the total score. Average test-retest correlation is 0.69 (van Zelst et al., 2003a).

The Beck Depression Inventory-II (BDI-II) was used to quantify symptoms of depression. This 21-item questionnaire addresses the severity of depression in the past week conform DSM-IV-TR criteria (Beck et al., 1996). With a scale of 0–3 for each item, a maximum score of 63 could be obtained. Higher BDI-II scores represent more severe depressive symptoms. A cutoff score of 13.5 (sensitivity=0.81, specificity=0.92) was used to identify above threshold symptoms of depression. The BDI-II has a Cronbach's alpha of 0.91 and the test-retest reliability of 0.96 (Beck et al., 1996).

2.3. Demographic characteristics and pre-existing psychopathology

Baseline characteristics were prospectively collected during the DECS trial and retrieved from the parent trial database. This included education, intoxications, (i.e., smoking, alcohol or substance use), EuroSCORE (Nashef et al., 1999), duration of the surgical procedure, type of surgery, length of ICU stay, ICU readmission, prolonged mechanical ventilation, postoperative corticosteroid use, and history of psychopathology (i.e., presence of depression, bipolar disorder, and anxiety disorders) (Dieleman et al., 2012).

2.4. Trait anxiety and childhood trauma

The State-Trait Anxiety Inventory Trait scale (STAI-T) was used to assess trait anxiety of the participants (Kvaal et al., 2005). Individual differences in intensified state anxiety as reaction to (potential) threatening events are addressed by 20 items on a 4-point Likert scale. A maximum score of 80 can be obtained, where higher scores indicate higher trait anxiety (Barnes et al., 2002). Cronbach's alpha ranged from 0.73 to 0.97; the test-retest reliability between 0.73 and 0.86 (Kvaal et al., 2005; Barnes et al., 2002).

The Childhood Trauma Questionnaire (CTQ) assesses five dimensions of trauma (i.e., physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect) during childhood and adolescence (Bernstein et al., 2003). The 28 items are scored on a 5-point Likert scale, and the five dimension scores add up to a maximum score of 125. A higher score indicates higher levels of childhood trauma. Median internal consistency reliability coefficients range from 0.66 to 0.92 (Thombs et al., 2009). Good test-retest reliability of 0.79 to 0.86 has been reported (Thombs et al., 2009). In previous literature, the emotional neglect dimension score was leading in different populations and highly correlated with the total score (Kok et al., 2016b). Since factors with highest potential impact on PTSD and depression scores were selected for the present study, the total emotional neglect dimension score was used in the statistical analyses.

2.5. DNA preparation and genotyping

The participants collected saliva at home (by chewing on a cotton

roll for two minutes) with the Genotek OG-500 Salivette, which they received by mail. 1111 Salivettes were returned, and subsequently labeled and stored. After shipping the Salivettes at −80 °C, DNA extraction was performed using Kleargene extraction chemistry and the Kompetitive Allele Specific PCR (KASP) genotyping assay was conducted to genotype the samples (LGC Genomics, London, United Kingdom). Single nucleotide polymorphisms (SNPs) of the glucocorticoid receptor (GR; i.e., rs41423147, rs6189, and rs10052957) previously reported to be associated with symptoms of PTSD and depression were included in this study (Thombs et al., 2009; Koper et al., 2014). The SNPs are in low linkage disequilibrium with r^2 values ranging from 0.015 to 0.065. In 1090 (87.6%) samples DNA extraction was successful and the call rates per SNP are listed in Supplementary Table S1. Genotype distributions of the SNPs were comparable to frequencies found in previous literature (Sherry et al., 2001). There was no evidence of particular genetic selection in this study population, and all distributions of all polymorphisms were in Hardy-Weinberg equilibrium (HWE).

2.6. Statistical analysis

Relevant demographic and clinical characteristics were reported using descriptive statistics. In previous studies, the impact of different factors separately on the occurrence of PTSD and depression symptoms was assessed (Gibbison et al., 2015; Lewisohn et al., 2000; Spertus et al., 2003; Klein et al., 1999; Kok et al., 2016b). Based on these results and the existing literature, a selection of variables was made to investigate to what extent these variables could explain variation in symptoms of PSTD and depression: advanced age, sex, dexamethasone administration (vs. placebo), history of substance use, pre-existing psychopathology, CTQ emotional neglect total dimension score, STAI-T total score, and genotypes of GR SNPs rs41423147, rs6189, and rs10052957. In accordance with our previous investigations (Kok et al., 2016a), several interaction terms were also introduced (i.e., [dexamethasone *x* female sex], [dexamethasone *x* rs41423147], [dexamethasone *x* rs6189], and [dexamethasone *x* rs10052957]). Incomplete genotyping cases were deleted list-wise (i.e., cases with missing genotype data were excluded). Complete case analysis was performed, and continuous SRIP and BDI-II scores were used as outcome measures. For both outcome measures, linear backwards regression analysis was performed, and the percentage variance that was explained by the model was assessed as R^2. At first, all potential factors were placed in the model, and contribution to the model was assessed by the significance value of the *t*-test for each variable. This significance value was then compared against the removal criterion (i.e., $p\text{-value}_{out}>0.10$), and the factor was removed from the model when this removal criterion was met. After this, the model with the remaining variables was re-estimated. Assumptions for multivariable regression analysis were met and stability of the models was examined by assessment of model fit, multicollinearity, homoscedasticity, and independent errors. Sensitivity analyses were conducted by adjusting the removal criterion value (i.e., $p\text{-value}_{out}>0.15$) to obtain an indication of model fit.

Findings with a p-value < 0.05 were considered statistically significant. All analyses were conducted using IBM Statistical Package for Social Sciences (SPSS Inc., version 20.0. IBM corp. Chicago, IL, USA).

3. Results

From the 1244 patients who had signed additional informed consent for the present study, 1111 (89.3%) returned the questionnaires and Salivettes by mail. Baseline characteristics (e.g., age, sex, type of surgery, and comorbidities) and a study enrolment flow diagram are presented in Table 1 and Fig. 1, respectively.

As reported elsewhere, symptoms of PTSD and depression were present in respectively 10.5% and 13.1% of the patients; 7.0% of patients had symptoms of both.[11] PTSD symptoms were assessed in 972 complete cases (89.1% of the total study sample); the full model is shown in Supplementary Table S2, which could explain 57% of the variance (R^2=0.57). After conducting linear backwards regression, trait anxiety and the [dexamethasone *x* female sex] interaction term were contained in the model and significantly influenced the proportion of variance in SRIP total score (Table 2). While higher trait anxiety scores increased SRIP total scores (i.e., development of PTSD symptoms), dexamethasone had the opposite effect in female patients (Table 2).

With regard to symptoms of depression, analyses of 944 complete cases (86.6% of the total study sample) showed that both trait anxiety and the [dexamethasone *x* female sex] interaction term also affected proportion of variance of BDI-II total scores (R^2=0.58, Supplementary Table S3). Again, higher trait anxiety contributed to the occurrence of depressive symptoms, whereas dexamethasone lowered BDI-II total scores in female patients. Moreover, older age was associated with depressive symptoms (Table 3).

Adjustment of the selection criterion did not alter the results with regard to both SRIP and BDI-II total scores.

Table 1
Demographic characteristics (N = 1090)[a].

Patients who received dexamethasone	553 (50.7)
Age, median (IQR), y	69.5 (62.9–76.0)
Male sex	868 (79.6)
Height, median (IQR), cm	175 (170–181)
Weight, median (IQR), kg	82 (73–92)
Low level of education[b]	597 (54.8)
Intoxications	
Smoking	100 (9.2)
Alcohol	863 (79.2)
Substance use	4 (0.4)
Pre-existing medical conditions	
Alzheimer's disease	4 (0.4)
Cancer	52 (4.8)
COPD	112 (10.3)
Hypertension	485 (44.5)
Diabetes mellitus	
Insulin dependent	38 (3.5)
Non-insulin dependent	124 (11.4)
Cerebrovascular events	
Stroke	37 (3.4)
Transient ischemic attack	41 (3.8)
Parkinson's disease	2 (0.2)
Peripheral artery disease	82 (7.5)
Pre-existing psychiatric conditions[c]	
Depression	22 (2.0)
Bipolar disorder	6 (0.6)
Anxiety disorder	17 (1.6)
EuroSCORE[d], median (IQR)	4 (3–6)
Presence of high trait anxiety[e]	931 (85.4)
Presence of childhood trauma[f]	201 (18.4)
Type of surgery	
Isolated CABG	391 (35.9)
CABG plus valve	207 (19.0)
Single valve	233 (21.4)
Multiple valves	18 (1.7)
Other	241 (22.1)
ICU LOS, median (IQR), h	21 (19–24)
First ICU admission	892 (81.8)

Abbreviations: EuroSCORE, European System for Cardiac Operative Risk Evaluation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; ICU LOS, intensive care unit length of stay.

[a] Data shown as number (%) of 1090 completely genotyped cases, unless reported otherwise.

[b] Low education ranges from no education to lower vocational education.

[c] Baseline inventory by self-report questionnaire.

[d] Higher scores represent increased perioperative mortality risk.

[e] State-Trait Anxiety Inventory Trait score above 39.

[f] Childhood Trauma Questionnaire (Emotional Neglect domain) score above 15.

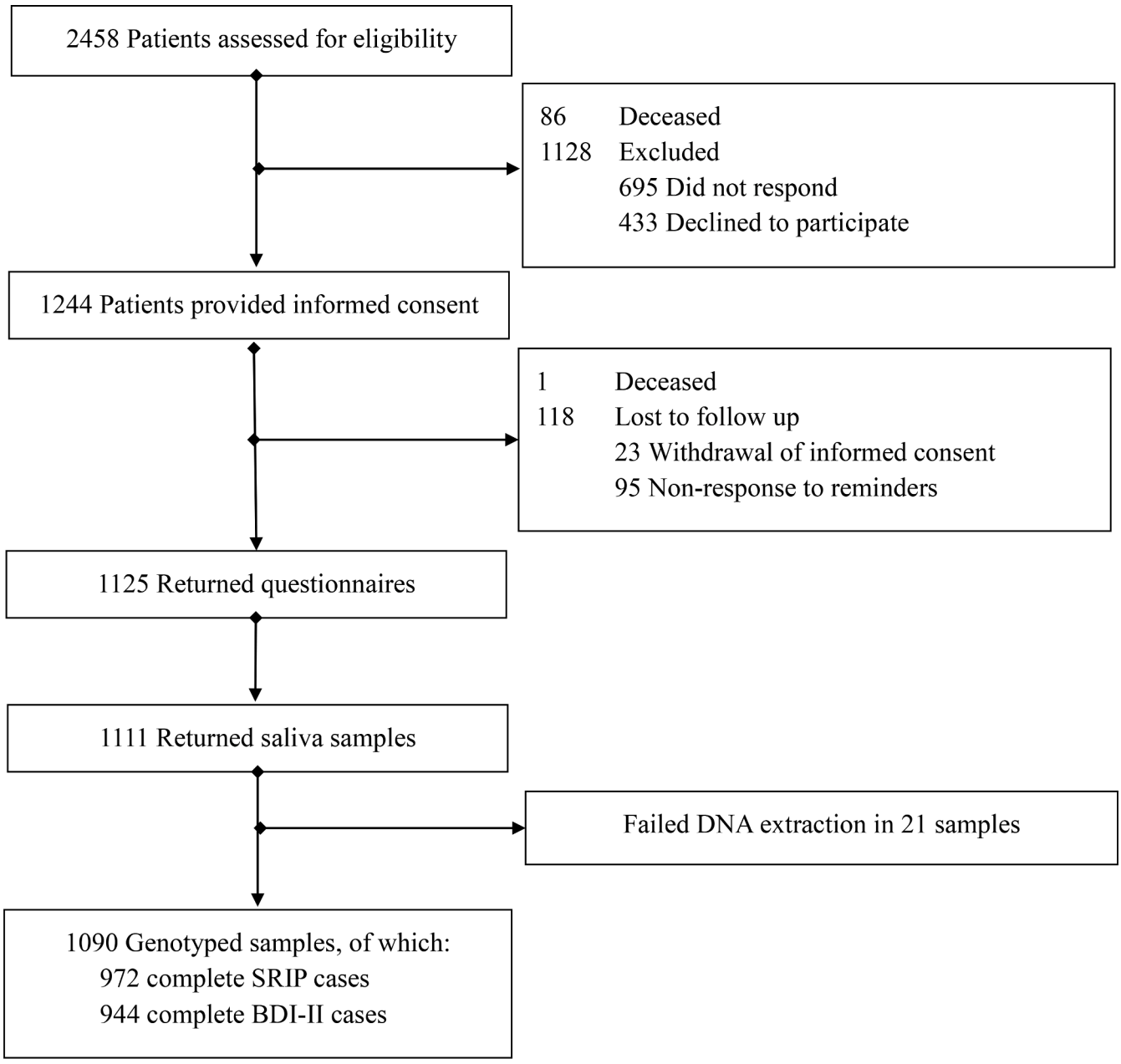

Fig. 1. Study enrollment flow diagram.
Abbreviations: SRIP, Self-Report Inventory for Post-traumatic stress disorder; BDI-II, Beck Depression Inventory-II.

Table 2
Linear backwards regression of factors associated with PTSD symptoms[a].

Factor	B	95% CI for B	ß	*p*	R^2	Adjusted R^2
Dexamethasone	1.085	−0.810 to 2.980	.074	.261	–	–
Female sex	.581	−0.469 to 1.630	.033	.278	–	–
Dexamethasone *x* female sex	−0.498	−0.834 to −0.161	−0.061	.004	–	–
Trait anxiety	.603	.570 to 0.636	.754	<0.001	–	–
Model summary	–	–	–	–	.570	.569

Abbreviations: B, unstandardized b-value; 95% CI for B, 95% confidence interval for unstandardized b-value; ß, standardized beta-value; *p*, p-value; R^2, proportion of explained variance.
[a] Complete case analysis, $n = 972$.

4. Discussion

This study aimed to investigate among those factors earlier found to be associated with psychopathology after cardiac surgery and ICU treatment, those that contributed most strongly to the variance, using a backwards regression model. We found trait anxiety to be consistent and important in this setting; patients with higher trait anxiety tended to develop more symptoms of both PTSD and depression, up to 4 years after

Table 3
Linear backwards regression of factors associated with depressive symptoms [a].

Factor	B	95% CI for B	ß	*p*	R^2	Adjusted R^2
Age	.035	.008 to 0.062	.054	.010	–	–
Dexamethasone	1.062	−0.637 to 2.761	.081	.220	–	–
Female sex	.300	−0.628 to 1.228	.019	.525	–	–
Dexamethasone *x* female sex	−0.416	−0.718 to −0.113	−0.057	.007	–	–
Trait anxiety	.539	.510 to 0.568	.762	<0.001	–	–
Model summary	–	–	–	–	.582	.580

Abbreviations: B, unstandardized b-value; 95% CI for B, 95% confidence interval for unstandardized b-value; ß, standardized beta-value; *p*, p-value; R^2, proportion of explained variance.
[a] Complete case analysis, $n = 944$.

hospital discharge. Furthermore, there is evidence that dexamethasone decreased PTSD and depression symptoms in female patients. Higher age was associated with the development of more depressive symptoms, but it did not affect the occurrence of PTSD symptoms.

For both symptoms of PTSD and depression, higher trait anxiety was the strongest determinant. Measurement of trait anxiety could therefore provide useful information when evaluating a patient's susceptibility to develop psychopathology after ICU admission (Kapsdorfer et al., 2018; Castillo et al., 2016; Jones et al., 2001). Furthermore, it could be used in the context of – preventive – interventions (e.g., cognitive behavioral therapy, educational programs, combinations of psychological interventions and medications) (Clark et al., 2003; Krasner et al., 2009; Jackson et al., 2012). However, this has never been tested before and it might be a too laborious tool for the clinical (ICU) setting.

Both pre-clinical and clinical studies point towards the existence of a vulnerability-stress model, in which predisposition to stress-related disorders (e.g., depression, PTSD) and the ability to cope later in life are linked to differential susceptibility. The following factors possibly contribute to this susceptibility; personality traits (e.g. trait anxiety), events earlier in life (e.g. childhood trauma, substance use), and genetic factors all contribute (Homberg and Jagiellowicz, 2021). Of note is that childhood trauma – and particularly emotional neglect – affects the development of psychopathology, especially when facing a new, severely stressful event (Kok et al., 2016b). In our study it did not contribute to the occurrence of PTSD and depression symptomatology after cardiac surgery and ICU stay. This was also the case for other factors concerning (psychiatric) medical history (i.e., pre-existing psychopathology and substance use), suggesting that trait anxiety effectively captures information from these domains.

Administering a large dose of dexamethasone intravenously during cardiac surgery results in cortisol suppression during this stressful event. By affecting the hypothalamic-pituitary-adrenal (HPA) axis response, this could relate to the occurrence of affective disorder symptoms later on (Heim et al., 2000). The intraoperative administration of dexamethasone proved to have a protective effect on symptoms of PTSD in female patients who underwent cardiac surgery and subsequent ICU treatment (Kok et al., 2016a). Recent studies suggest this effect to be influenced by common genetic variants of the glucocorticoid receptor (GR) (Cruz-Topete et al., 2019; Scheimann et al., 2019). However, in the process of backwards linear regression, genetic factors did not contribute to the variability in psychopathology symptoms even though it was significantly associated in our previous investigations. A similar discrepancy is present for depressive symptoms (Gibbison et al., 2015; Lewinsohn et al., 2000). This might be due to surpass effect of trait anxiety regarding the vulnerability model as described earlier (Homberg et al., 2021).

Our study has several strengths. First, the large sample size and uniformity of this randomized cardiac surgery cohort is unique. Moreover, the majority of study participants returned validated questionnaires and call rates of genetic information were high. Also, our analyses provide a comprehensive and practical view on the multifactorial base of the development of psychopathology after cardiac surgery and intensive care treatment.

Limitations of this study include the assessment of psychopathology through validated questionnaires, rather than clinical interview by a psychologist or psychiatrist. Furthermore, variability in the level of detail of different variables assessed, remains a point of particular interest. Most factors were collected very thoroughly, but pre-existing psychopathology and interventions or complications during the follow up period were measured in less detail. This also includes the use of psychotropic medication and beta blockers throughout the study period, presumably resulting in incomplete and therefore less reliable information. Nevertheless, modeling factors in this way represents clinical practice, contributing to the relevance and applicability of our results. Comparison of our results in a replication set could further enhance this understanding.

In conclusion, we found that most of the variation in psychopathology symptoms after cardiac surgery is explained by higher trait anxiety female sex, age, and dexamethasone use. Female cardiac surgery patients may benefit from intraoperative dexamethasone administration, however, validation of these results is necessary to ascertain their reproducibility, generalizability, and clinical applicability.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Role of the Sponsor

The funding agencies did not contribute to the study design, the collection, analysis, and interpretation of data, the writing of the manuscript, or the decision to submit the paper for publication. The authors declare no conflict of interest.

Author statement

Lotte Kok wrote the first draft of the manuscript and undertook the statistical analyses. Manon Hillegers, Dieuwke Veldhuijzen, Marian Joëls, Jan Dieleman and Diederik van Dijk designed the study and wrote the protocols. Marco Boks, Christiaan Vinkers and Arjen Slooter provided input and support regarding the statistical analyses, the interpretation of results and the discussion section. All authors contributed to and have approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2021.100199.

References

Barnes, L.L.B., Harp, D., Lung, W.S., 2002. Reliability generalization of scores on the Spielberger State-Trait Anxiety Inventory. Educ. Psychol. Meas. 62, 603–618. https://doi.org/10.1177/0013164402062004005.

Beck, A.T., Steer, R.A., Ball, R., et al., 1996. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. J. Pers. Ass. 67, 588–597. https://doi.org/10.1207/s15327752jpa6703_13.

Bernstein, D.P., Stein, J.A., Newcomb, M.D., et al., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child. Abus. Negl. 27, 169–190. https://doi.org/10.1016/s0145-2134(02)00541-0.

Castillo, M.I., Cooke, M.L., Macfarlane, B., et al., 2016. In ICU state anxiety is not associated with posttraumatic stress symptoms over six months after ICU discharge: a prospective study. Aust. Crit, Care. 29, 158–164. https://doi.org/10.1016/j.aucc.2015.09.003.

Clark, D.M., Ehlers, A., McManus, F., et al., 2003. Cognitive therapy versus fluoxetine in generalized social phobia: a randomized placebo-controlled trial. J. Consult. Clin. Psychol. 71, 1058–1067. https://doi.org/10.1037/0022-006X.71.6.1058.

Cruz-Topete, D., Oakley, R.H., Carroll, N.G., et al., 2019. Deletion of the cardiomyocyte glucocorticoid receptor leads to sexually dimorphic changes in cardiac gene expression and progression to heart failure. J. Am. Heart. Assoc. 8, e011012 https://doi.org/10.1161/JAHA.118.011012.

Dieleman, J.M., Nierich, A.P., Rosseel, P.M., et al., 2012. Intraoperative high-dose dexamethasone for cardiac surgery a randomized controlled trial. JAMA 308, 1761–1767. https://doi.org/10.1001/jama.2012.14144.

Gibbison, B., Spiga, F., Walker, J.J., et al., 2015. Dynamic pituitary-adrenal interactions in response to cardiac surgery. Crit. Care. Med. 43, 791–800. https://doi.org/10.1097/CCM.0000000000000773.

Hauer, D., Weis, F., Papassotiropoulos, A., et al., 2011. Relationship of a common polymorphism of the glucocorticoid receptor gene to traumatic memories and posttraumatic stress disorder in patients after intensive care therapy. Crit. Care. Med. 39, 643–650. https://doi.org/10.1097/CCM.0b013e318206bae6.

Heim, C., Ehlert, U., Hellhammer, D.H., 2000. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinol 25, 1–35. https://doi.org/10.1016/s0306-4530(99)00035-9.

Homberg, J.R., Jagiellowicz, J., 2021. A neural model of vulnerability and resilience to stress-related disorders linked to differential susceptibility. Mol. Psychiatry. https://doi.org/10.1038/s41380-021-01047-8. Online ahead of print.

Hovens, J.E., Bramsen, I., van der Ploeg, H.M., et al., 2000. Test-retest reliability of the self-rating inventory for posttraumatic stress disorder. Psycho. Rep. 87, 735–737. https://doi.org/10.2466/pr0.2000.87.3.750.

Jackson, J.J., Hill, P.L., Payne, B.R., et al., 2012. Can an old dog learn (and want to experience) new tricks? Cognitive training increases openness to experience in older adults. Psychol. Aging. 27, 286–292. https://doi.org/10.1037/a0025918.

Jones, C., Griffiths, R.D., Humphris, G., et al., 2001. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. Crit. Care. Med. 29, 573–580. https://doi.org/10.1097/00003246-200103000-00019.

Kapsdorfer, D., Hlavacova, N., Vondrova, D., et al., 2018. Neuroendocrine response to school load in prepubertal children: focus on trait anxiety. Cell. Mol. Neurobiol. 38, 155–162. https://doi.org/10.1007/s10571-017-0544-7.

Klein, D.N., Schatzberg, A.F., McCullough, J.P., et al., 1999. Age of onset in chronic major depression: relation to demographic and clinical variables, family history, and treatment response. J. Aff. Dis. 55, 149–157. https://doi.org/10.1016/s0165-0327(99)00020-8.

Kok, L., Hillegers, M.H., Veldhuijzen, D.S., et al., 2016a. The effect of dexamethasone on symptoms of posttraumatic stress disorder and depression after cardiac surgery and intensive care admission: longitudinal follow-up of a randomized controlled trial. Crit. Care Med. 44, 512–520. https://doi.org/10.1097/CCM.0000000000001419.

Kok, L., Sep, M.S., Veldhuijzen, D.S., et al., 2016b. Trait anxiety mediates the effect of stress exposure on post-traumatic stress disorder and depression risk in cardiac surgery patients. J. Aff. Dis. 2016, 216–223. https://doi.org/10.1016/j.jad.2016.07.020.

Koper, J.W., van Rossum, E.F.C., van den Akker, E.L.T., 2014. Glucocorticoid receptor polymorphisms and haplotypes and their expression in health and disease. Steroids 92, 62–73. https://doi.org/10.1016/j.steroids.2014.07.015.

Krasner, M.S., Epstein, R.M., Beckman, H., et al., 2009. Association of an educational program in mindful communication with burnout, empathy, and attitudes among primary care physicians. JAMA 302, 1284–1293. https://doi.org/10.1037/a0025918.

Kvaal, K., Ulstein, I., Nordhus, I.H., et al., 2005. The Spielberger State-Trait Anxiety Inventory (STAI): the state scale in detecting mental disorders in geriatric patients. Int. J. Geriatr. Psychiatry. 7, 629–634. https://doi.org/10.1002/gps.1330.

Lewinsohn, P.M., Rohde, P., Seeley, J.R., et al., 2000. Natural course of adolescent major depressive disorder in a community sample: predictors of recurrence in young adults. Am. J. Psychiatry. 157, 1584–1591. https://doi.org/10.1176/appi.ajp.157.10.1584.

Nashef, S.A.M., Roques, F., Michel, P., et al., 1999. European system for cardiac operative risk evaluation (EuroSCORE). Eur. J. Cardiothorac. Surg. 16, 9–13. https://doi.org/10.1016/s1010-7940(02)00208-7.

Scheimann, J.R., Moloney, R.D., Mahbod, P., et al., 2019. Conditional deletion of glucocorticoid receptors in rat brain results in sex-specific deficits in fear and coping behaviors. Elife 8, e44672. https://doi.org/10.7554/eLife.44672.

Schelling, G., Richter, M., Roozendaal, B., et al., 2003. Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. Crit. Care Med. 31, 1971–1980. https://doi.org/10.1097/01.CCM.0000069512.10544.40.

Sherry, S.T., Ward, M.H., Kholodov, M., et al., 2001. dbSNP: the NCBI database of genetic variation. Nucl. Acids. Res. 29, 308–311. https://doi.org/10.1093/nar/29.1.308.

Spertus, I.L., Yehuda, R., Wong, C.M., et al., 2003. Childhood emotional abuse and neglect as predictors of psychological and physical symptoms in women presenting to a primary care practice. Child. Abus. Negl. 27, 1247–1258. https://doi.org/10.1016/j.chiabu.2003.05.001.

Spijker, A.T., van Rossum, E.F.C., 2012. Glucocorticoid sensitivity in mood disorders. Neuroendocrinol 95, 179–186. https://doi.org/10.1159/000329846.

Stoll, C., Schelling, G., Goetz, A.E., et al., 2000. Health-related quality of life and post-traumatic stress disorder in patients after cardiac surgery and intensive care treatment. J. Cardiothor. Surg. 120, 505–512. https://doi.org/10.1067/mtc.2000.108162.

Tedstone, J.E., Tarrier, N., 2003. Posttraumatic stress disorder following medical illness and treatment. Clin. Psychol. Rev. 23, 409–448. https://doi.org/10.1016/s0272-7358(03)00031-x.

Thombs, B.D., Bernstein, D.P., Lobbestael, J., et al., 2009. A validation study of the Dutch Childhood Trauma Questionnaire-short form: factor structure, reliability, and known-groups validity. Child. Abus. Negl. 33, 518–523. https://doi.org/10.1016/j.chiabu.2009.03.001.

Yehuda, R., 2000. Post-traumatic stress disorder. NEJM 346, 108–114. https://doi.org/10.1056/NEJMra012941.

Yehuda, R., Halligan, S.L., Golier, J.A., et al., 2004. Effects of trauma exposure on the cortisol response to dexamethasone administration in PTSD and major depressive disorder. PNEC 29, 389–404. https://doi.org/10.1016/s0306-4530(03)00052-0.

van Zelst, W.H., de Beurs, E., Beekman, A.T.F., et al., 2003a. Criterion validity of the self-rating inventory for posttraumatic stress disorder (SRIP) in the community of older adults. J. Aff. Dis. 76, 229–235. https://doi.org/10.1016/s0165-0327(02)00095-2.