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IR PSICHOFARMAKOLOGIJA

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CONTENTS
TURINYS

Dear colleagues,

I am very happy to present you the latest issue of Biological Psychiatry and Psychopharmacology.

A prospective study by Dirgyte and Baniene found that depressive and anxiety symptoms are highly common among parents of children diagnosed with cancer. This is among a few studies from Lithuania focused on mental health problems in family members of cancer patients. The study findings indicate that psychological problems of parents caring for their children with cancer should not be ignored and vigorously addressed. Further studies investigating psychological problems and potential clinical value of stress management interventions in parents of children diagnosed with cancer and other severe chronic diseases are strongly warranted.

Muranovaite with colleagues reported that 3-week session of Mindfulness based practice was effective in patients with Somatoform Autonomic Dysfunction of cardiological system. The study contributes to the growing body of evidence that Mindfulness based practice has numerous beneficial effects and its wider implementation in clinical settings should be strongly considered

A systematic review by Zalyte and colleagues demonstrated that exposure method (traditional in vivo exposure vs. virtual reality exposure) used in cognitive behavioral therapy for panic disorder does not affect treatment outcomes. Authors recommended that further high-quality studies investigating most optimal exposure method should be attempted.

Bagdonaite and Steibliene found that the risk for developing cognitive impairment/dementia was low in Lithuanian medical workers. Long duration of education and intensive cognitive activity in free time were the most prevalent preventing factors of developing future cognitive decline. Education intervention can be employed to improve mental health status among medical professionals.

Juskiene and co-authors reported that nearly one-third of women with coronary artery disease met diagnostic criteria for obstructive sleep apnea; however, its severity was not associated with anxiety nor depression symptoms.

On behalf of Editorial board I would like to thank authors and reviewers for their valuable contributions.

Sincerely,

Adomas Bunevicius, MD, PhD

Editor in Chief

Biological Psychiatry and Psychopharmacology

Effects of Low-Dose Mindfulness-Based Practice on Patients with Somatoform Autonomic Dysfunction of Cardiovascular System

Mažo intensyvumo įsisąmoninimu grįstų praktikų efektyvumas pacientams sergantiems širdies ir kraujagyslių sistemos somatoformine autonomine disfunkcija

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SUMMARY

Introduction. Mindfulness based practice (MBP) might positively influence cardiovascular disease risk via an indirect pathway including change in emotion regulation. However, this link, to the best of our knowledge, was never tested in patients with Somatoform Autonomic Dysfunctionof cardiological system (SADCS).

Objective. This study investigated associations between cardiovascular disease risk reduction (measured by heart rate variability [HRV]) and change in depression symptoms in SADCS patients during 3 weeks of MBP.

Methods. The study consisted of a run-in session (consultation and diagnosis by the cardiologist), baseline and final sessions (assessment of physiological and psychological data) before and after three weeks of MBP or waiting. Seventeen of the randomly assigned participants (age 32±10) with SADCS completed a three-week MBP and entered into the experimental group while twelve participants (age 39±13) were randomly assigned to a waiting-list control group. For both groups psychological (Hospital Anxiety and Depression Scale [HADS], Perceived Stress Scale [PSS-10], Five facet mindfulness Questionnaire [FFMQ] and Patient Health Questionnaire – 15 [PHQ-15]) and physiological measures (central aortic blood pressure (cABP) and root mean square of the successive differences [RMSSD]) were assessed at baseline and final sessions.

Results. Results indicated larger differences in depression symptoms for participants engaged in 3 weeks of MBP when compared to control group (Mdn = –1, interquartile = –2–0 vs, Mdn = 0, interquartile 0–1.75, U = 46, p = 0.028, r = 8.85). Change in RMSSD scores for the experiment group was significantly higher when compared to control group (M=11.58, SD = 17.81 vs. M = –1.95, SD = 12.3, t(27) = –2.33, p = 0.028, d = .88). Correlation was observed between change in depression symptoms and RMSSD in the treatment group, (β = 0.687, p = 0.005) but not in control group (p >.05).

Conclusions. The change in depression scores for participants engaged in three weeks of MBP were significantly greater when compared to control group. Changes in RMSSD scores for the experiment group were significantly higher than for the control group. A significant correlation between HRV and depression symptoms was found only in the treatment group.

Keywords: Somatoform autonomic dysfunction, Mindfulness, Depression, Anxiety, Heart rate variability.

SANTRAUKA

Įvadas. Įsisąmoninimu grįstos praktikos (ĮGP) veikdamos emocijų reguliavimą gali sumažinti širdies ir kraujagyslių sistemos ligų riziką. Tačiau, mūsų žiniomis, emocijų reguliavimo sąsajos su širdies ir kraujagyslių sistemos ligų rizikos veiksniais niekada nebuvo tirta pacientų sergančių širdies ir kraujagyslių sistemos somatoformine autonomine disfunkcija (ŠKSSAD) imtyje.

Tikslas. Šio tyrimo tikslas – nustatyti sąsajas tarp širdies ir kraujagyslių sistemos ligų rizikos veiksnių (remiantis širdies dažnio variabilumo rodikliais) ir depresijos simptomų pokyčių pacientams dalyvaujantiems trijų savaičių ĮGP programoje ir sergantiems ŠKSSAD.

Metodai. Tyrimą sudarė trys sesijos: pirma sesija (kardiologo konsultacija ir diagnozė), bazinė ir galutinė sesijos (psichologinių bei fiziologinių veiksnių vertinimas) prieš ir po trijų savaičių ĮGP arba laukimo. Eksperimentinę grupę sudarė 17 atsitiktine tvarka atrinktų tiriamųjų (amžius – 32±10 m.), sergančių ŠKSSAD ir baigusių trijų savaičių ĮGP programą. Dvylika dalyvių (amžius – 39±13 m. buvo atsitiktinai atrinkti ir paskirti į laukiančiųjų sąrašo kontrolinę grupę. Abiejų grupių tiriamųjų psichologiniai ir fiziologiniai veiksniai vertinti tyrimo pradžioje ir po trijų savaičių ĮGP programos. Psichologiniai veiksniai buvo vertinti Ligoninės nerimo ir depresijos klausimynu (angl. *Hospital Anxiety and Depression Scale, HADS*), Suvokiamo streso klausimynu (angl. *Perceived Stress Scale, PSS-10*), Penkių dėmesingo įsisąmoninimo aspektų klausimynu (F*ive facet mindfulness Questionnaire, FFMQ*) ir Pacientų sveikatos klausimynu – 15 (angl. *Patient Health Questionnaire, PHQ-15*). Buvo atlikti centrinio (aortos) kraujo spaudimo ir kvadratinės šaknies iš gretimų NN intervalų skirtumų (RMSSD) fiziologiniai matavimai.

Rezultatai. Pacientų, tris savaites taikiusių IGP, grupėje depresiškumo lygis mažėjo labiau nei kontrolinėje grupėje (Mdn = –1, interkvartiliai = –2–0 vs. Mdn = 0, interkvartiliai 0–1,75, U = 46, p = 0,028, r = 8,85). RMSSD pokytis eksperimentinėje grupėje buvo reikšmingai didesnis lyginant su kontroline grupe (M = 11,58, SD = 17,81 vs. M = –1,95, SD = 12,3, t(27) = –2,33, p = 0,028, d = 0,88). Aptikta sąsaja tarp depresiškumo lygio pokyčio ir RMSSD eksperimentinėje, (β = 0,687, p = 0,005), bet ne kontrolinėje grupėje (p >0,05).

Išvados. Tris savaites vykdžiusių ĮGP pacientų grupėje depresijos simptomų lygis mažėjo labiau lyginant su kontroline grupe. Širdies dažnio variabilumo pokyčiai eksperimentinėje grupėje buvo didesni nei kontrolinėje grupėje. Tik grupėje atlikusioje ĮGP pastebėta sąsaja tarp širdies dažnio variabilumo ir depresijos simptomų stiprumo.

Raktažodžiai: Somatoforminė autonominė disfunkcija, dėmesingumas, depresija, nerimas, širdies dažnio variabilumas.

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INTRODUCTION

A number of previous studies have demonstrated that as much as one-third of physical symptoms in medical care are medically unexplained symptoms and that these somatic symptoms are associated with an economical burden on the health system and society because of enormous consumption of health resources and reduction in the quality of patients' lives [1-4]. If untreated in the long run, functional medically unexplained symptoms develop into structural changes of the cardiovascular system and present cardiovascular disease risk, causing negative cardiovascular outcomes, such as atrial fibrillations, strokes and infarcts of vasospastic origin [5, 6].

Research shows that Mindfulness Based Cognitive Therapy (MBCT) is a low-cost and effective intervention for patients with somatization, improving their life quality and reducing the health service burden in general [7]. However, the mechanism of mindfulness interventions for Somatoform Autonomic Dysfunction (SAD) patients seeking cardiological treatment is not well understood.

In a review of mindfulness and cardiovacular disease risk, Loucks and colleagues (2015) propose a plausible mechanism for associations of mindfulness with positive cardiovascular outcomes (Figure 1) [8]. In short, Loucks et al. (2015) explain that mindfulness interventions positively influence cardiovascular disease risk via an indirect pathway including change in: a) emotion regulation; b) attention control; and c) self-awareness [8]. Indeed, numerous imaging studies reveal MBCT atributted changes in gray matter concentration of brain regions (such as left hippocampus, posterior cingulare cortex, temporo-parietal junction and cerebellum) associated with emotion regulation, learning, memory and self-referential processing [9;10]. However, the proposed link between MBCT affected emotional regulation (in depression or anxiety disorders) and cardiovascular disease risk is less explored. Indeed, depression is the one of the most common comorbidities of somatoform disorder [11;12] and has been known as a factor associated with lowered HRV [13]. This direct top-down link between central nervous system and heart rate variability (HRV) allows for indexing the central-peripheral integration, organismic self-regulation, and thus better autonomous nervous system condition [14]. Thus, in a simplified version of Loucks et al. (2015) model for SAD patients we would expect that MBCT effect on emotion regulation primarily would be visible in changes of depressive mood [8]. Then, if changes persist for a certain time this would generally affect HRV. While the proposed linkage might sound too reductionistic to the best of our knowledge it was never explored in a scientific literature. Confirming such links would allow future studies to investigate which aspects of MBCT affected emotional regulation contribute to lower depression symptoms.

Therefore, our study aimed investigating if there are associations between Mindfulness Based Practice (MBP) and cardiovascular disease risk reduction in patients diagnosed with Somatoform Autonomic Dysfunction of cardiological system (SADCS) through change in depression symptoms. Our primary aim was to measure if 3 weeks of MBP results in change in depression symptoms and whether change in depression symptoms influence HRV. The secondary aim was to measure if 3 weeks of MBP results in changes in mindfulness, somatic symptom severity, anxiety, and stress.

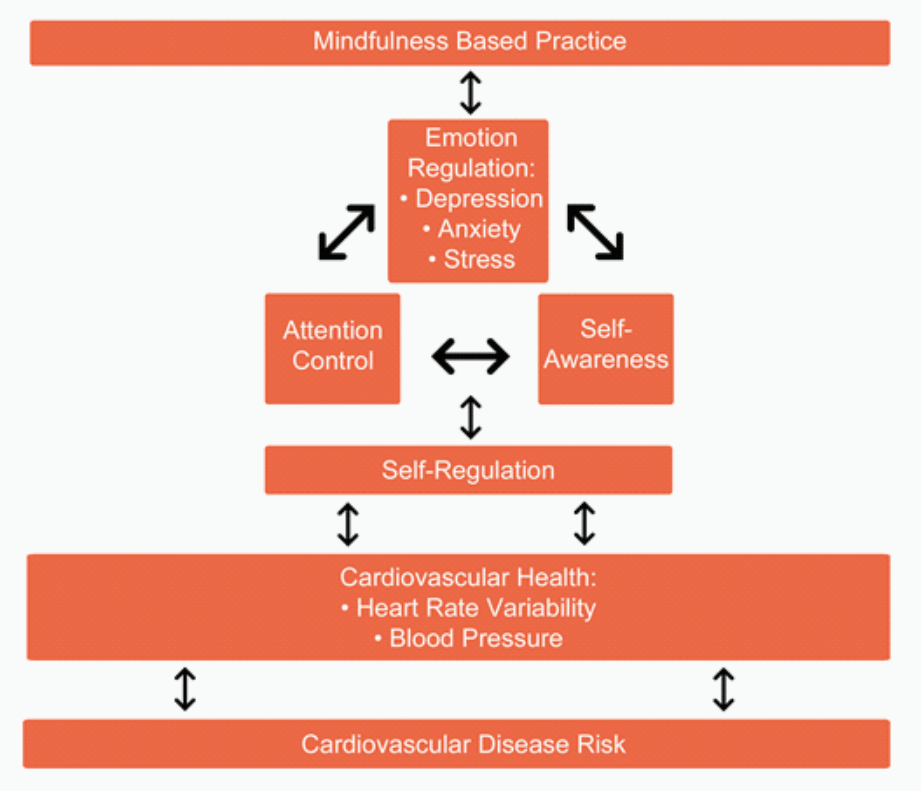

Figure 1. **Conceptual framework suggesting possible mindfulness based practice mechanisms influencing cardiovascular disease risk factors**

METHODS

Participants

Participants were recruited from a secondary health care facility specializing in cardiology. They were informed verbally and in written form about all pertinent aspects of the study. Informed consent was obtained from all participants, and the study was approved by the Institutional Review Board of LCC International University and performed in accordance with the Helsinki Declaration.

The sample consisted of participants diagnosed with SADCS by a cardiologist. Diagnosis was established by a cardiologist after performing ultrasonography; cardiac stress test (stationary exercise ergometer); 24-hour arterial blood pressure monitoring (if deemed necessary); thyroid check-up (if deemed necessary). Eligibility criteria are presented in table 1. Inclusion criteria were: diagnosed with SADCS (F45.31); between 18 and 60 years old; signed written informed consent form (ICF); fluency in Lithuanian. Exclusion criteria were: structural cardiovascular disease or any other structural disease affecting autonomic balance (e.g. hypothyroidism); current practice of meditation; current use of beta blocker, benzodiazepine or any other pharmacological treatment known to have affect on cardiovascular system.

A total of 48 potential participants were screened by a cardiologist, 39 subjects met inclusion criteria and continued into the baseline session (V1), 29 participants agreed to participate by signing an ICF. In sum, 17 of the randomly assigned participants completed a three-week MBP program (where mindfulness was practiced for 15 minutes daily) and entered into the experimental group. Twelve participants were randomly assigned to a waiting-list control group. For both groups psychological and physiological measures were assessed at baseline (V1) and final session (V2). Mean age of the study sample was 36 years (SD = 12) and the sample was comprised of 65.5% females and 34.5% males.

Psychological Outcome Measures

Hospital anxiety and depression scale (HADS). Anxiety and depression symptoms were measured using HADS [15]. The scale is used widely in Lithuania [16] and is reported to be a valid measure in assessing anxiety and depression symptom severity in patients with coronary artery disease [17], as well as psychiatric, and primary care patients [18]. Cronbach's alpha for HADS in this study was .87 for 14 items.

Perceived Stress Scale (PSS-10). Perceived Stress Scale (PSS-10) is a 10 item self-administered scale assessing appraisal of perceived stress. It is reliable and valid instrument measuring experienced stress levels [19]. Validity and reliability study of the scale in Lithuanian sample presented a Cronbach's apha of .840 [20]. Cronbach's alpha of PSS-10 for the population of this study was .89 for 10 items.

Five facet mindfulness questionnaire (FFMQ). Five facet mindfulness questionnaire is a tool based on previously existing mindfulness questionnaires developed by Baer, Smith, Hopkins, Krietemeyer, & Toney (2008), measuring observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience and is one of the most commonly used methods for assessing mindfulness [21]. Construct validity study involving meditator and non-meditator groups supported validity of FFMQ and showed mindfulness facets being significantly related to meditation experience, psychological symptoms and well-being [21]. Cronbach's alpha for the given sample was .79 for 39 items.

Patient Health Questionnaire (PHQ-15). Somatic symptoms severity was measured using the PHQ-15 questionnaire. Patient Health Questionnaire is a widely used short version of Primary Care Evaluation of Mental Disorders questionnaire, developed from a collaboration of psychological health specialists and general practitioners [22]. PHQ-15 is a self-administered questionnaire allowing for screening for somatoform disorders and assessing somatic symptoms and their severity. PHQ-15 contains symptoms related to heart rate and pain however lacks symptoms relating to arterial blood pressure (ABP). Considering the nature of SADCS "unstable blood pressure" is added to the Lithuanian version as symptom number 16 to the scale. A systematic review of PHQ-15 concluded that this is a valid measure for assessing and monitoring somatization [23]. In the given sample Cronbach's alpha for PHQ-15 was .79 for 16 items.

Physiological data collection. Central aortic blood pressure (cABP) was measured using the Mobil-O-Graph monitor. This device fulfills the validation recommendations of the British Hypertension Society, which concludes that the device is meets accuracy requirements and can be used for clinical use [24]. For HRV measures the time domain measure of root mean squared successive differences (RMSSD) were obtained using the HeartMath emWave monitor (version 2.2.5.4876; HeartMath LLC, 2012). HRV data analyses were conducted using the Kubios HRV software (version 2.2; University of Eastern Finland, 2014). A recording of 6.5 minutes was trimmed approximately 20 seconds from front and back in order to have a stable 5-minute recording for each participant. No manual corrections were performed. In order to be provided with an artifact-free recording artifact correction

Table 1. **Eligibility Criteria**

Inclusion Criteria		Exclusion Criteria	
EL1	Able to speak Lithuanian;	EX1	Structural cardiovascular disease or any other structural disease affecting autonomic balance (e.g. hypothyroidism);
EL2	Age between 18 and 60 years old;	EX2	Current practice of meditation;
EL3	Diagnosed with Somatoform Autonomic Dysfunction of Heart and Cardiovascular System (F45.31);	EX3	Current treatment with beta blockers, benzodiazepines or other medication known to have affect on cardiovascular system;
EL4	Signed written informed consent (ICF).	EX4	Participants who withdraw consent.

was set to medium level. Setting artifact correction to medium level rather than low level might have reduced variability, however for the purpose of ectopy-free data the medium level was used for analysis.

Study design

The study consisted of three sessions: initial run-in session (consultation and diagnosis at the cardiologist's office), baseline session (assessment of physiological and psychological data and brief mindfulness training based session for treatment group), and final session (assessment of physiological and psychological data) after three weeks. A list of participant numbers was generated before the baseline session and all participants were randomly assigned ("random.org", 2015) to either treatment or waiting-list group before attending the baseline session. Both physiological and psychological data were collected in a procedural room of a clinic. Participants were asked to abstain from food for two hours and stimulant drinks for 24 hours before data recording. HRV measures were taken in a seated position, approximately at the same time of day, on the same ear lobe/arm under same conditions in the same environment: in the procedural room while watching a relaxing nature video for 6.5 minutes.

Mindfulness based meditation exercise. The intervention in this study was based on two formal MBCT and MBSR practices: body scan and sitting meditation. Three different practices were audio-recorded by a certified MBCT and MBSR instructor. A website holding the guided meditations for the three weeks including a short online diary under each practice was set up. Participants in the experiment group were instructed to complete a 15-minute practice for 6 days each week for the three-week period starting from the next day after baseline session. Participants were also asked to record experiences of each practice in the online-diary, indicating how involved they were on a scale from 0% to 100%. Reports with participants' logs and their initials were automatically sent to the investigators' emails.

Statistical Analyses

The IBM SPSS 21 statistical analysis software was used to analyze the data. Independent samples t-test and Mann-Whitney U test were used for examining differences in HRV and depression symptoms between control and experiment groups after 3 weeks of MBP. Dependent samples t-test and Z-Wilcoxon tests were used to assess differences in change in mindfulness, somatic symptom severity, anxiety, stress and depression within groups. In addition, Spearman's rank-order correlation was used in assessing relationships between change in depression symptoms and change in HRV variables.

Two outliers with standard deviations above 3 were excluded (one due to abnormally high depression scores, who was referred to a psychiatrist, and another due to abnormally high RMSSD values, who was referred to a cardiologist for further assessment).

RESULTS

The data are presented as mean±SD for normally distributed values and as median and interquartiles for non-normally distributed data. Descriptive statistics for both wait-list control and MBP treatment groups are presented (see Table 2).In short, the total sample was comprised of 17 participants in treatment group (13 females and 4 males), mean age 31.6 years (SD 9.8) and 12 in waiting-list control group (6 females and 6 males), mean age 38.9 (SD 12.9).

Changes in symptoms of depression, anxiety, perceived stress, mindfulness, medically unexplained symptoms, HRV and blood pressure at pre- and post-assessment in both groups are presented in Table 3. A Mann-Whitney U test was performed on the change in depression symptoms between control and experiment groups. Differences in depression symptom score changes for participants engaged in 3 weeks of MBP were significantly lower when compared to control group (Mdn = –1, interquartile = –2–0 vs. Mdn = 0, interquartile = 0–1.75, U = 46, p =0.028, r = 8.85).

An independent sample t-test was performed on the change in RMSSD between control and experiment groups and indicated that after the 3 weeks of MBP the change in RMSSD scores for the experiment group was significantly higher when compared to control group (M = 11.58, SD = 17.81 vs. M = –1.95, SD = 12.3, t(27) = –2.33, p = 0.028, d = .88).Further analysis using a Wilcoxon Signed-ranks test indicated that RMSSD was significantly higher in the treatment group at V2 (post MBP) compared to V1 (pre MBP) (Mdn = 55.1, interquartile = 34.4–63.6 vs. Mdn = 43.9, interquartile = 31.3–56.1, Z = –2.16, p = 0.031, r = 0.56).

Spearman's rank-order correlation was used to determine the relationship between change in depression symptoms and change in RMSSD for both groups. Analysis showed a statistically significant correlation between change in depression symptoms and RMSSD in the treatment group, Spearman's r(15) = 0.687, p = .005 but not in group of control subjects (p>0.05).

Change in mindfulness, somatic symptom severity, anxiety, stress and depression in experiment group was assessed comparing values at V1 and V2 using paired samples t-test and Wilcoxon Signed-ranks tests for normally distributed and non-normally distributed data respectively. A paired-samples t-test indicated that mindfulness was significantly higher in the treatment group at V2 (post MBP) compared to V1 (pre MBP) (M = 3.38, SD = 0.49 vs. M = 3.2, SD = .46), t(15) = –1.98, p = 0.068, d = .38). Stress was marginally significantly lower only in treatment group at V2 (post MBP) compared to V1 (pre MBP) (M = 15.1, SD = 7.86 vs. M = 17.8, SD = 6.93, t(15)= 2.12, p = 0.053, d = .36). Depression symptoms had also significantly decreased in treatment group at V2 (post MBP) (Mdn = 2, interquartile = 1–6) compared to V1 (pre MBP) (Mdn= 4, interquartile = 1–7), U = –2.25, p = 0.024, r = 0.58. Medically unexplained symptom severity significantly decreased both in wait-list control group at V2 (post MBP) compared to V1 (pre MBP) (M = 7.58, SD = 4,44 vs. M = 10.3,

Table 2. **Descriptive Characteristics of the Sample**

Measure	Minimum	Maximum	Mean	SD
Age	21	59	35.9	12.1
Height	158	193	172.2	9.6
Weight	52	125	75.2	17.5
Body mass index	20.1	36.1	25.1	4.2

Table 3. **Between-group analysis: Changes in symptoms of depression, anxiety, perceived stress, mindfulness, medically unexplained symptoms, HRV and blood pressure at pre and post-assessment in both groups.**

Variable	Control (n=12)			Treatment (n=15)			% Change Between group *t/U value	*p value
	Pre Mean/Mdn (SD/Interquartile)	Post Mean/Mdn (SD/Interquartile)	% Change	Pre Mean/Mdn (SD/Interquartile)	Post Mean/Mdn (SD/Interquartile)	% Change		
Depression (HADS)	3.0(.25–5.75)	3.5 (2.0–6.5)	0 (0–1.75)	4.0 (1.0–7.0)	2.0 (1.0–6.0)	–1 (–2–0)	46	0.028
Anxiety (HADS)	9.25(4.59)	7.42 (3.87)	–1.83 (1.75)	11.1 (4.54)	7.87 (4.82)	–3.2 (2.81)	1.55	0.135
Stress (PSS-10)	17.75 (7.48)	16.75 (8.23)	–1 (5.31)	17.73(6.93)	15.1 (7.86)	–2.67 (4.88)	0.84	0.410
Mindfulness (FFMQ)	3.13(.34)	3.11(.44)	–.02 (.27)	3.20 (.46)	3.38 (.49)	.18 (.35)		
SSS (PHQ-15)	10.25 (5.66)	7.58 (4.44)		10.3 (4.73)	6.8 (4.49)		0.59	0.562
RMSSD	44.3 (37.4–70)	46.8 (42.4–61.7)	–1.95 (12.3)	43.9 (31.3–56.1)	55.1 (34.6–63.6)	11.6 (17.8)	–2.33	0.028
ABP systolic	121.83 (10.99)	123.58 (13.75)	1.75 (10.1)	123.9 (15.8)	118. (12.4)	–5.93 (11.6)	1.84	0.078
ABP diastolic	79 (8.01)	77.25 (5.82)	–1.75 (6.27)	77.3 (12.3)	73.9 (13.4)	–3.47 (10.2)	0.54	0.596
cABP systolic	110.25 (9.28)	112.42 (12.52)	2.17 (8.40)	112.1 (15.2)	108.5 (13.7)	–3.53 (9.48)	1.66	0.111
cABP diastolic	80.33 (7.84)	78.75 (5.72)	–1.5 (–5.5–2.5)	78.7 (12)	75.4 (13.1)	–3 (–8–3)	86.5	0.864

SD = 5.66, t(12) = 2.62, p = 0.024, d = 0.52), and the treatment group at V2 (post MBP) compared to V1 (pre MBP) (M = 6.8, SD = 4.49 vs. M = 10.3, SD = 4.73, t(15) = 3.83, p = 0.002, d = 0.75). In addition, anxiety also significantly decreased both in the wait-list control group at V2 (post MBP) compared to V1 (pre MBP) (M = 7.42, SD = 3.87 vs. M = 9.25, SD = 4.59, t(12) = 3.63, p = 0.004, d = 0.43), and the treatment group at V2 (post MBP) compared to V1 (pre MBP) (M = 7.87, SD = 4.82 vs. M = 11.1, SD = 4.54,t(15) = 4.41, p = 0.001, d = 0.68).

DISCUSSION AND CONCLUSIONS

The primary purpose of this study was to measure if three weeks of MBP results in change in depression symptoms. We found that the change in depression scores for participants engaged in three weeks of MBP were significantly greater after the three week MBP practice when compared to control group. Our second aim was supported, as changes in RMSSD scores for the experiment group were significantly higher after the 3 weeks of MBP when compared to the control group. What is more, a significant correlation between RMSSD and depression symptoms was found only in the treatment group, suggesting a relationship between change in depression symptoms and RMSSD changes.

In fact, neuropsychological perspective could help us interpret the observed associations. Variety of psychological disorders including depression are associated with prefrontal cortex hypoactivity and error in the inhibitory processes resulting in hyperactive amygdala, poor executive functioning and emotional regulation [25]. Davidson (2000) states that prefrontal cortex activity is inversely related to subcortical structures, such as amygdala and Lane with colleagues (2001) associates prefrontal cortex activity with HRV [26; 27]. Thayer & Brosschot stress the link between prefrontal cortex hypoactivity, amygdala hyperactivity and low HRV arguing an obvious connection between cognitive and autonomic dysregulation [14]. Thus MBP affecting depression might primarily influence emotional regulation and follow-on affecting HRV measures.

The secondary aim was to measure if three weeks of MBP results in changes in anxiety symptoms, symptom severity, stress, and mindfulness. It was found that mindfulness was significantly higher only in the treatment group at V2 (post MBP) compared to V1 (pre MBP) and stress was marginally significantly lower only in the treatment group at V2 (post MBP) when compared to V1 (pre MBP). In contrast, anxiety and stress symptom changes were similar in both treatment and control groups. Anxiety and somatic symptoms severity significantly decreased for both groups at V2 (post MBP) compared to V1 (pre MBP). However, although not significant, the decrease in somatic symptom severity was higher in treatment group as compared to control. The reduction in symptom severity and anxiety in both groups may be explained by the fact that both groups were informed about the diagnosis and educated about SAD. It is believed that diagnosis of SAD and assurance of absence of any organic dysfunction may have reduced anxiety and stress symptoms related with somatic symptomology.

Research shows that mindfulness is an effective treatment for a variety of anxiety and mood disorders and is especially effective in reducing depression, anxiety, and stress symptoms

[28, 29]. We believe that our study extended these findings by showing that MBP not only influences symptoms of depression but also (through change in depression) positively influence HRV. This in turn might lower cardiovascular disease risk longitudinally. However long term cardiovascular disease risk management was beyond the scope of our study and requires further investigation.

Strengths, limitations and future directions. It is considered that a specific sample, randomization of subjects and well-validated outcome measure instruments are among the major strengths of the current study. Despite our consistent results there are limitations of this study. The major limitation of the study is a small sample size and unequal group sizes might have affected results of this study. Due to a limited number of subjects extreme scores might have influenced the results. Research shows that pre-existing low HRV is a representative of low flexibility and adaptability and perseverance [32]. The pre-existing group and participant differences might have also affected results. Participants that start with a relatively high HRV may reduce variance. Further research might benefit from matching groups for baseline HRV levels, socio-demographic variables such as gender, age, and others. Another limitation is that the MBP intervention was limited to a minimum of three-weeks. Research conducted by Klatt, Buckworth and Malarkey (2008) on a low dose mindfulness program (20 minutes of practice for 6 weeks) reported significant reductions in perceived stress and increases in mindfulness [30]. However, according to Baer, Carmody & Hunsinger (2012) significant changes in mindfulness occur at the second week of practice whereas changes in stress occur at the fourth week of practice in a full 8-week MBSR program [31]. The intervention in this study was limited to 15 minutes of practice per day. It is suggested that further research would explore dose-dependent effects of MBP by manipulating the number of minutes practiced per day and the number of weeks spent in the program. Another limitation concerns treatment compliance. Average practice compliance was 80.7 minutes per week (SD = 20.8) among the experiment group. Average time practiced per week in Baer et. al. (2012) study examining weekly mindfulness change was 227 minutes [31]. Whereas average time practiced in our study was 73 minutes, which is approximately a third less.

The majority of experimental condition participants subjectively reported that their health became better in terms of lowered symptoms of depression, anxiety, stress and ABP. We want to emphasize, that high levels of depression, anxiety, stress and somatic symptoms found for patients diagnosed with SADCS in this study provide solid ground for the necessity for an effective and low-cost intervention to decrease symptomology, regulate autonomic nervous system and lower cardiovascular disease risk for SAD patient group. In light of the literature and visible trends of this study, we conclude that further studies with improved methodology and design would greatly benefit the population with SAD and the society in general.

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Depression, anxiety and stress coping in parents of children with the oncological disease

Tėvų, slaugančių onkologine liga sergančius vaikus, depresiškumas, nerimas ir streso įveika

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SUMMARY

Background. Illness of the child and caring causes plenty difficulties which affect parents' psychological well-being. However, studies evaluating depression, anxiety and stress coping in parents of children with oncological diseases in Lithuania are lacking.

The aim of the study was to establish the severity of depression, anxiety and their relations with the use of stress coping strategies among parents of children with the oncological disease.

Methods. The study involved 80 parents of children with diagnosed oncological disease, who at the time of the survey were hospitalized in the clinics of Kaunas and Santariškės. The questionnaire consisted of sociodemographic indicators and questions about depression and anxiety symptoms, suicidality, the use of stress coping strategies.

Results. 42.5% of participants had mild, moderate or severe depression symptoms and 72.5% parents had increased anxiety symptoms. There were significant differences ($p<0.05$) between groups with and without depression symptoms and averages of using such stress coping strategies as self-distraction, active coping, denial, behavioral disengagement, positive reframing, humor, acceptance, self-blame. In groups of with and without anxiety symptoms, there were significant differences ($p<0.05$) between averages of such stress coping strategies as denial, venting, planning, acceptance, religion, self-blame use.

Conclusions. Almost half of parents have mild, moderate or severe depressive symptoms and two-thirds of parents have mild, moderate or severe anxiety symptoms. Parents who have expressed depressiveness signs more often use denial, behavioral disengagement, self-blame strategies and less self-distraction, active coping, positive reframing, humor, acceptance than parents without depressiveness signs. Parents with expressed anxiety symptoms more often use denial, venting, planning, religion, self-blame strategies and less acceptance strategy than parents without anxiety symptoms.

Keywords. Depression, anxiety, stress coping strategies, parents, children, oncological disease.

SANTRAUKA

Įvadas. Vaiko liga ir slaugymas sukelia daugybę sunkumų, kurie paveikia tėvų psichologinę savijautą. Vis tik Lietuvoje trūksta tyrimų apie depresijos, nerimo simptomų pasireiškimą ir streso įveiką tarp tėvų, kurių vaikai serga onkologine liga.

Tikslas – nustatyti tėvų, kurių vaikai serga onkologine liga, depresijos bei nerimo paplitimą ir sąsajas su naudojamomis streso įveikos strategijomis.

Metodika. Apklausta 80 tėvų, kurių vaikams diagnozuota onkologinė liga ir kurie apklausos metu buvo hospitalizuoti Kauno arba Santariškių klinikose. Klausimynas sudarytas iš socialinių-demografinių rodiklių bei klausimų apie depresijos, nerimo simptomus, polinkį į suicidą, naudojamas streso įveikos strategijas.

Rezultatai. 42,5 proc. tiriamųjų turi lengvus, vidutinio sunkumo arba sunkius depresijos simptomus ir 72,5 proc. tėvų turi išreikštus nerimo simptomus. Turinčių ir neturinčių depresiškumo požymius grupėse statistiškai reikšmingai ($p<0,05$) skiriasi tokių streso įveikos strategijų naudojimo vidurkiai kaip savęs išblaškymo, aktyvaus įveikimo, neigimo, elgesio pakeitimo, pozityvaus pakeitimo, humoro naudojimo, priėmimo, savęs kaltinimo. Nustatyta, kad turinčių ir neturinčių nerimo simptomus grupėse statistiškai reikšmingai ($p<0,05$) skiriasi tokių streso įveikos strategijų naudojimo vidurkiai kaip neigimo, ventiliavimo, planavimo, priėmimo, atsigręžimo į religiją, savęs kaltinimo.

Išvados. Beveik pusė tėvų turėjo lengvus, vidutinio sunkumo arba sunkius depresijos simptomus ir du trečdaliai tėvų turėjo lengvus, vidutinio sunkumo arba sunkius nerimo simptomus. Turintys depresiškumo požymius tėvai dažniau naudoja neigimo, elgesio pakeitimo, savęs kaltinimo strategijas ir rečiau savęs išblaškymo, aktyvaus įveikimo, pozityvaus pakeitimo, humoro naudojimo, priėmimo strategijas nei tėvai, kurie neturi depresiškumo požymių. Tėvai, kurie pasižymi išreikštais nerimo požymiais, dažniau naudoja neigimo, ventiliavimo, planavimo, atsigręžimo į religiją, savęs kaltinimo strategijas ir rečiau priėmimo strategiją palyginus su nepasižyminčiais padidėjusiu nerimu tėvais.

Raktažodžiai. Depresiškumas, nerimas, streso įveikos strategijos, tėvai, vaikų onkologinės ligos

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INTRODUCTION

According to World Health Organization, cancer has According to World Health Organization, cancer has become one of the leading causes of morbidity [1]. Consequently, there are growing attention to prevention of oncological diseases and assistance to people suffering from the cancer diagnosis. Although cancer diagnosis is more frequent to older people, there are no exceptions to youngsters. Fortunately, a cancer diagnosis for a child is quite rare with 200 suffering of one million children or 200 thousands new cases worldwide [2,3]. According to National Cancer Institute in Lithuania, there were 60 new cases of cancer diagnosis and 15 deaths of cancer among children between 0 and 14 years in 2012 [4]. Analyzing 29 Europe countries reassuring tendencies observed in improving survival, especially in Eastern Europe [5].

Despite rarity and positive trends in survival, there is a huge shock for parents about their child' cancer diagnosis. Long-term hospitalization is followed by stress and difficulties and is defined as medical trauma [6]. It is common among carers, especially parents. Increased risk of emotional difficulties such as depression and enlarged anxiety is evaluated [7, 8]. Moreover, reactions and adjustment of parents affect and is associated with children reaction to illness [9].

Dealing with stressors as illness people tend to choose and use some ways of behavior or thinking which are defined as coping. In some countries, programs based on psychoeducation are used for parents to learn about coping and more adaptive stress coping strategies [10]. Concerning these examples, there is a need to analyze stress coping in a specific background and find more adaptive stress coping strategies to reduce the severity of depression and anxiety symptoms. Some international studies include stress coping and emotional difficulties of parents, but there is a lack of study which involves various localizations, prognosis of cancer, both gender parents or not only those who are looking for financial support [11, 12, 13]. Moreover, it is not known about the adjustment and adaptation of parents dealing with children cancer in Lithuania.

The aim of the study was to establish the severity of depression, anxiety and their relations with the use of stress coping strategies among parents of children with the oncological disease.

METHODS

Study population

The study was approved by the Bioethics Committee of Lithuanian University of Health Sciences (No. BEC-SP(B)-32). Eighty parents (93% response rate) voluntarily agreed to participate in this study and signed a written informed consent form. Selection criteria in this study were: parenting child from birth to 18 years old, the oncological disease is diagnosed for a child, a child is hospitalized in clinics of Kaunas or Santariškės, speaking fluently in the Lithuanian language. Data were collected from December of 2015 to May of 2016 during visits to divisions for children with onco-hematological diseases, where researchers introduced the aim and questionnaires to fill.

Assessment

The questionnaire consisted of the Hospital Anxiety and Depression (HAD) Scale [14, 15], the Brief COPE scale [16], questions about suicidality, sociodemographic characteristics, features of children' illness.

The HAD scale as the self-reported instrument is used for evaluation of depressive or anxiety symptoms and their severity. It consists of 14 questions, which are combined into two subscales (depression and anxiety) with seven questions. Each item is rated from 0 to 3 and scores of subscales range from 0 to 21. 0–7 scores mean normal level of anxiety or mood, 8–10 – mild depressive or anxiety symptoms, 11–14 – moderate, 15–21 – severe depressive or anxiety symptoms. The HAD scale is a useful and easy instrument with established reliability and validity [17, 18] to detect mood or anxiety disorders in non-psychiatric people [19] or to use for assessment in psycho-oncology [20] and parents of children with oncological disease [21]. The internal consistency (Cronbach's alpha) of HADS was 0.92 (for anxiety sub-scale was 0.9 and for depression sub-scale was 0.84).

The Brief COPE scale is used for assessment of stress coping strategies and is made of 14 sub-scales with 2 questions: Self-distraction, Active coping, Denial, Substance use, Use of emotional support, Use of instrumental support, Behavioral disengagement, Venting, Positive reframing, Planning, Humor, Acceptance, Religion, Self-blame. Each item rated as 1 ("I haven't been doing this at all"), 2 ("I've been doing this a little bit"), 3 ("I've been doing this a medium amount") or 4 ("I've been doing this a lot"). Higher scores indicate a greater level of the use. This instrument is a shorter version of stress coping with established reliability and validity [16] and is also used for assessment of parents [22, 23, 24, 25]. The double-sided translation of Brief COPE scale to the Lithuanian language was made with permission of the author and by independent translators. Translations were reviewed by researchers and the final version was used in the study. Cronbach's alfa for Brief COPE was 0.71 (for each subscale varied from 0.59 to 0.95).

Authors' designed sociodemographic and children' illness questionnaire consisted of 11 questions: age, gender, residence, education, marital status, working status of respondents, financial sufficiency for care and age, time after diagnosis, type and stage of diagnosis of a child with the illness. Complementary questions about suicidality were: "Did you ever thought about suicide during the illness of your child?", "Did you ever planned your suicide during the illness of your child?" "Did you ever attempted suicide during the illness of your child?".

Statistical analysis

All statistical analyses were performed using "IBM SPSS Statistical version 20.0". The descriptive analysis was presented as means and standard deviation for continuous data and percentages for categorical data. The sample size of the study was relatively small, so non-parametric tests used to compute statistical analysis. Associations between having or not having depression or anxiety symptoms and the use of stress coping strategies were assessed using Mann-Whitney U test. Statistical significance level was set at 5% ($p<0.05$).

RESULTS

The final sample consisted of 80 parents. Sociodemographic characteristics and features of children' illness are presented in Table 1.

11.3% (n = 9) parents thought about suicide during the

Table 1. **Sociodemographic characteristics of 80 parents and features of their children' illness**

Respondents' (n=80):	
Age (min-max, mean±SD)	24–55, 37.5±7.45
Gender, n (%)	
Male	23 (28.7%)
Female	57 (71.3%)
Residence, n (%)	
City	44 (55%)
Town or village	36 (45%)
Education, n (%)	
Higher	43 (53.8%)
Non-higher	37 (46.3%)
Marital status, n (%)	
Having partner	64 (80%)
Without partner	16 (20%)
Working status, n (%)	
Working	22 (27.5%)
Not working	58 (72.5%)
Financial sufficiency for care, n (%)	
Sufficiently	38 (47.5%)
Not sufficiently	42 (52.5%)
Childen' with illness:	
Age (min-max, mean±SD)	1–18, 7.3±4.78
Type of diagnosis, n (%)	
Oncohematological	38 (47.5%)
Neurooncological and other types	42 (52.5%)
Stage of diagnosis, n (%)	
I or II	17 (21%)
III or IV	21 (26%)
Other or do not know	42 (53%)
Time (months) after diagnosis (min-max, mean±SD)	1–96, 7.9±15.51

illness of a child and 3.8% (n = 3) had plans to suicide during the illness of a child, but all participants didn't try to attempt suicide.

The depression subscale of HADS varied from 0 to 19 scores with total mean 7.2±4.25. The scoring in the anxiety sub-scale of HADS is from 1 to 20 with total mean 10.7±4.79. The evaluation of depressive or anxiety symptoms and their severity is shown in Figure 1.

After grouping mild, moderate and severe symptoms into one group, 72.5% (n = 58) of parents had anxiety symptoms and 27.5% (n = 22) didn't have anxiety symptoms, 42.5% (n = 34) of participants had depression symptoms and 57.5% (n = 46) didn't have depression symptoms. These groups were compared with groups of parents' sociodemographic characteristics and features of their children' illness (see Table 1), but there were no significant differences in groups ($p>0.05$).

Having (depression or anxiety subscale of HADS scoring is ≥8) depression or anxiety symptoms and not having (depression or anxiety subscale of HADS scoring is ≤7) depression or anxiety symptoms groups were also invoked for associations between depressiveness or anxiety and the use of stress coping strategies.

It was found that parents who had depression symptoms more often used such stress coping strategies as denial, behavioral disengagement, self-blame, while parents who hadn't expressed depression symptoms more often used self-distraction, active coping, positive reframing, humor, acceptance (Table 2).

Parents with a normal level of anxiety more often used acceptance than parents with occurring anxiety symptoms. Parents who had expressed anxiety symptoms more often used denial, venting, planning, religion, self-blame strategies (Table 3).

DISCUSSION

The diagnosis and treatment of childhood oncological disease can affect psychological well-being, daily routine, responsibilities, roles of both parents and there are an increasing number of studies with both genders of participants [26]. In our study, most of the participants were women, while men – less than a third. In other studies, there was a similar proportion in gender [6, 13, 21, 25, 26, 27] or men were eliminated from assessment because of severe availability [28, 29]. These comparisons can be considered as no essential differences between cultures when mothers more tend to choose the role of carer and fathers to become least involved and spend their time providing family financially.

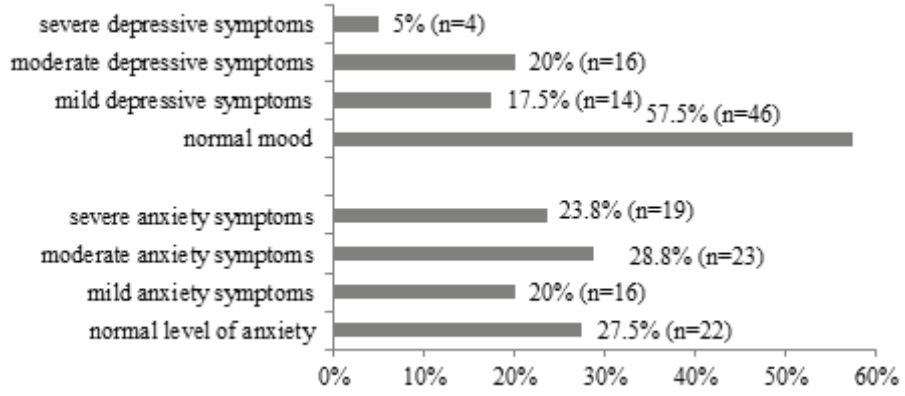

Figure 1. **The evaluation of depressive or anxiety symptoms and their severity among parents**

Table 2. **The use of stress coping strategies between the groups of parents with and without depression symptoms**

Stress coping strategies	Not having depression symptoms (N=46)		Having depression symptoms (N=34)		P
	Mean±SD	Mean Rank	Mean±SD	Mean Rank	
Self-distraction	5.2±1.50	46.85	4.2±1.23	31.91	**0.004***
Active coping	6.6±1.60	45.55	5.9±1.18	33.66	**0.019***
Denial	3.2±1.53	34.98	4.0±1.43	47.97	**0.010***
Substance use	2.3±0.94	40.30	2.3±0.84	40.76	0.884
Use of emotional support	4.6±1.41	42.90	4.3±1.36	37.25	0.258
Use of instrumental support	5.1±1.27	44.40	4.5±1.33	35.22	0.070
Behavioral disengagement	3.2±1.62	35.08	4.1±1.68	47.84	**0.011***
Venting	4.5±1.53	41.79	4.2±1.07	38.75	0.529
Positive reframing	4.9±1.85	46.39	3.7±1.68	32.53	**0.007***
Planning	5.1±1.67	41.57	4.9±1.57	39.06	0.627
Humor	2.9±1.19	44.41	2.5±1.21	35.21	**0.037***
Acceptance	7.1±1.08	49.01	5.9±1.32	28.99	**<0.001****
Religion	4.4±2.00	41.51	4.2±2.02	39.13	0.643
Self-blame	3.1±1.48	28.83	5.4±1.78	56.29	**<0.001****

*p<0.05; **p<0.001

Our study revealed that almost half of parents had depression symptoms and two-thirds had increased anxiety symptoms. These findings are more expressed than in other studies [6, 8, 13, 21]. These differences could appear due to a certainly worse situation in Lithuania or different assessment instruments like STAI (The State-Trait Anxiety Inventory) or Beck depression scale [8, 13]. Moreover, in some studies, there was a different level of severity when considered as depression or anxiety manifestation [6, 21]. However, HADS subscales means were similar: in this study depression 7.2±4.3, while in others – 7±4.3 and 7.6±4.4, in this study anxiety 10.7±4.8, in others – 11±4.4 and 10±4.2 [6, 21]. That means, the situation is quite similar and despite different evaluation methods parents are in the risk group to experience psychiatric disorders. In addition, we found that some parents thought about suicide and have plans to attempt suicide.

Our study showed associations between expressed depression symptoms and more frequent use of denial, behavioral disengagement, self-blame strategies and less frequent use of self-distraction, active coping, positive reframing, humor, acceptance. Some of these relationships (behavioral disengagement, self-blame, active coping, humor, acceptance) were reported in other studies [11, 12, 13, 27], while some relationships (self-distraction, active coping) were

Table 3. **The use of stress coping strategies between groups of parents with and without increased anxiety symptoms**

Stress coping strategies	Not having anxiety symptoms (N=22)		Having anxiety symptoms (N=58)		P
	Mean±SD	Mean Rank	Mean±SD	Mean Rank	
Self-distraction	4.9±1.52	42.55	4.7±1.45	39.72	0.621
Active coping	6.3±1.81	42.20	6.3±1.33	39.85	0.676
Denial	2.9±1.44	31.18	3.8±1.51	44.03	**0.021***
Substance use	2.4±0.73	43.73	2.3±0.96	39.28	0.201
Use of emotional support	4.2±0.80	36.89	4.6±1.55	41.87	0.368
Use of instrumental support	4.7±1.12	38.50	4.9±1.40	41.26	0.623
Behavioral disengagement	3.2±1.92	32.59	3.8±1.59	43.50	0.051
Venting	3.9±1.21	30.57	4.6±1.36	44.27	**0.011***
Positive reframing	5.1±2.01	47.86	4.2±1.76	37.71	0.074
Planning	4.4±1.50	32.00	5.2±1.62	43.72	0.040*
Humor	2.8±0.96	45.80	2.7±1.29	38.49	0.135
Acceptance	7.1±1.23	50.50	6.4±1.31	36.71	**0.014***
Religion	3.6±1.82	30.89	4.7±1.99	44.15	**0.019***
Self-blame	3.0±1.91	25.48	4.5±1.85	46.20	**<0.001****

*p<0.05; **p<0.001

opposite to some studies [11, 12].

Having increased anxiety symptoms were associated with more frequent use of denial, venting, planning, religion, self-blame strategies and less frequent use of acceptance strategy. Similarly, some relationships (acceptance, self-blame, religion, planning) were reported in other studies [11,13,27]. We observed that some active stress coping strategies as venting, planning, religion is associated with increased anxiety and this could happen because of needed activity to invoke these strategies.

This study has some benefits as great response rate considering so few cases in Lithuania and possibly one of the first reports about parents' depression and increased anxiety symptoms, stress coping. Furthermore, stress coping strategies wasn't grouped in adaptive and maladaptive before a survey, so after results, we can see which is associated with expressed depression or increased anxiety symptoms. However, we do not know whether having mood or anxiety disturbances leads to choosing specific stress coping strategies or the use of specific strategies encourages the manifestation of depression or anxiety symptoms. Despite this, results provide a better view of parents' mental health and can be used in the development of support for this specific group or other relatives dealing with the oncological disease.

In terms of limitations of this study, included mild symptoms into grouping (having or not having expressed depression or increased anxiety symptoms) could reinforce the results of the evaluation. Moreover, some subscales of stress coping strategies showed poor internal reliability. This could happen because of shorter scale, which was chosen due to aspirational for better response rate and fever costs of time for parents. Recommendations for future studies are trying longitudinal study to see how the severity of depression and anxiety symptoms changes over time, using longer or several instruments for evaluation or choosing a qualitative method of study to find out more about parents' well-being, adjustment and coping.

CONCLUSIONS

Mild, moderate or severe depressive symptoms were found in almost half of parents. More frequent use of denial, behavioral disengagement, self-blame strategies was associated with expressed depression symptoms, while the less frequent use of self-distraction, active coping, positive reframing, humor, acceptance were more frequent among parents without depressiveness signs. Two-thirds of parents had expressed mild, moderate or severe anxiety symptoms and anxiety symptoms among parents were associated with more frequent use of denial, venting, planning, religion, self-blame strategies and less frequent use of acceptance strategy. These results suggest that psychoeducation about more adequate, appropriate stress coping may be useful to reduce depression and anxiety symptoms in parents of children with the oncological disease.

Conflicts of interest

Authors declare no conflicts of interest.

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Evaluation of medical workers according to the risk factors for developing cognitive impairment

Medicinos darbuotojų vertinimas pagal rizikos veiksnius kognityvinių funkcijų sutrikimui išsivystyti

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SUMMARY

Background. With the increasing of the life expectancy, the average age of practising medical workers in Lithuania has reached 49 years, and still the tendency towards life expectancy is continuing to increase. Therefore, cognitively healthy aging has been prioritised in Lithuania.

Objective. To evaluate the incidence of preventive and risk factors for developing cognitive impairment/ dementia among medical workers in Lithuania, and to predict this risk over a 20-year period.

Materials and methods: In total, 138 medical workers aged 50 years and older (89.9% were females) at three different medical institutions in Lithuania, participated in the cross-sectional study and filled in a questionnaire developed by authors (Bagdonaite E., Steibliene V.). The questionnaire included information about six risk factors that increase and four preventive factors that decrease the risk of developing cognitive impairment/dementia. The risk for developing cognitive impairment/dementia in 20 years was calculated using the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score.

Results. The one third of subjects (31.2%) had two risk-increasing factors. No more than two risk-increasing factors had 61.3% and no more than three – 79.1% of all subjects. The most frequent risk factor was arterial hypertension (37.0%), the rarest – type 2 diabetes mellitus (5.1%). All subjects had one preventive factor – education and the majority (42.0%) had two additional preventive factors. The most frequent preventive factor was cognitive activity (70.0%), the rarest – adherence to the Mediterranean diet (25.0%). The most frequent factor that determined high CAIDE risk scores was the absence of regular physical activity. The risk of 1% for developing cognitive impairment/dementia in 20 years was estimated for 61.6%, 1.9% risk for 34.1% and 4.2% risk for 4.3% medical workers.

Conclusions. Three-quarters of medical workers in Lithuania had no more than 3 risk-increasing factors for developing cognitive impairment/dementia, of which inheritance among the first line relatives was the most frequent. The majority of medical workers had 2 cognitive impairment/dementia risk-decreasing factors – long duration of education and intensive cognitive activity in free time. The risk of developing cognitive impairment/dementia in 20 years of lifetime among medical workers in Lithuania did not exceed 4.2%, however, this risk could be diminished by an increase in physical activity and adherence to the Mediterranean diet.

Key words: cognitive impairment, dementia, risk, medical workers, CAIDE

SANTRAUKA

Įvadas. Ilgėjant tikėtinai gyvenimo trukmei, vidutinis praktikuojančių medicinos darbuotojų amžiaus vidurkis Lietuvoje pasiekė 49 metus, bei stebima tendencija didėti. Todėl sveikas kognityvinis senėjimas tampa prioritetine tyrimų sritimi.

Tyrimo tikslas. Įvertinti kognityvinio sutrikimo/demencijos išsivystymo riziką didinančių ir mažinančių veiksnių dažnius tarp Lietuvos medicinos darbuotojų Lietuvoje bei nustatyti išsivystymo riziką per ateinančius 20 gyvenimo metų.

Metodai. Trijų Lietuvos gydymo įstaigų 138 medicinos darbuotojai, 50 metų amžiaus ir vyresni (89,9 proc. tiriamųjų – moterys), dalyvavo skersinio pjūvio dizaino tyrime ir užpildė autorių sudarytą klausimyną, kuriame vertinti šeši kognityvinio sutrikimo/demencijos išsivystymo riziką didinantys ir keturi riziką mažinantys veiksniai. Rizikos kognityviniam sutrikimui/demencijai išsivystyti per ateinančius 20 gyvenimo metų nustatymui naudota Kardiovaskulinių rizikos veiksnių, Senėjimo ir Demencijos (angl. *Cardiovascular Risk Factors, Aging and Dementia, CAIDE*) skalė.

Rezultatai. Viena trečioji tiriamųjų dalis (31,2 proc.) turėjo du riziką didinančius veiksnius. Ne daugiau dviejų riziką didinančių veiksnių turėjo 61,3 proc., ne daugiau trijų – 79,1 proc. tiriamųjų. Dažniausiai pasitaikantis rizikos veiksnys buvo arterinė hipertenzija (37,0 proc.), rečiausiai – II tipo cukrinis diabetas (5,1 proc.). Visi tiriamieji turėjo vieną riziką mažinantį veiksnį (išsilavinimo trukmę), bet beveik pusė tiriamųjų (42,0 proc.) taip pat turėjo du papildomus riziką mažinančius veiksnius. Dažniausiai nustatytas riziką mažinantis veiksnys buvo užsiėmimas kognityvine veikla (70,0 proc.), rečiausiai – mityba pagal Vidužemio jūros dietą (25,0 proc.). Dažniausiai pasitaikantis CAIDE balą didinantis rizikos veiksnys – reguliaraus fizinio aktyvumo nebuvimas. Demencijos išsivystymo rizika per 20 metų lygi 1 proc. buvo nustatyta 61,6 proc., 1,9 proc. rizika – 34,1 proc., 4,2 proc. rizika – 4,3 proc. tiriamųjų.

Išvados. Trys ketvirtadaliai Lietuvos medicinos darbuotojų turi ne daugiau trijų kognityvinio sutrikimo/demencijos riziką didinančių veiksnių, iš kurių dažniausias yra pirmos kartos paveldėjimas demencijos sutrikimui. Dauguma medicinos darbuotojų turi du riziką mažinančius veiksnius: ilgą išsilavinimo trukmę bei užsiėmimą intensyvia kognityvine veikla ne darbo metu. Lietuvos medicinos darbuotojų rizika kognityviniam sutrikimui/demencijai išsivystyti per ateinančius 20 gyvenimo metų yra ne didesnė nei 4,2%, bet koreguojant mažą fizinį aktyvumą ir laikantis Vidužemio jūros dietos principų, šią riziką būtų galima dar sumažinti.

Raktažodžiai: kognityvinių funkcijų sutrikimas, demencija**,** rizika**,** medicinos darbuotojai, CAIDE

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INTRODUCTION

According to the data of the World Health Organization (WHO), 47.5 million of world population were suffering from with dementia in 2016 [1]. The number of dementia cases in Lithuania was slightly higher than 47 thousand [2]. With the increasing of the life expectancy and the decreasing the rate of birth in most developed countries, the elderly people make a significant proportion of total population [3]. Therefore, a rise in prevalence of chronic diseases (including dementia) is expected. It is predicted that number of dementia patients will have exceeded 130 million in 2050 [4]. While dementia decreases life expectancy by 8.5 years on average, the biggest impact is laid on quality of life of patients themselves and their relatives, as well causing large economic burden to the society [5]. Alzheimer's disease (AD) is the most frequent type of dementia in the world, constituting around 60.0-80.0% of total diagnosed dementia cases. Vascular dementia (VD) comprises aproximately 10.0% of dementias [6], however this type of dementia is most often diagnosed in Lithuania [7]. Other types of dementia (dementia with Lewy bodies, frontotemporal dementia, mixed dementia, dementia in Parkinson's disease, Creutzfeldt-Jakob disease and etc.) constitute significantly lower part. Clinical-pathological studies show that mixed pathologies occur more often than various types of dementia separately, i.e. AD and VD, AD and dementia with Lewy bodies [8]. In addition to timely and effective pharmaceutical treatment, the prevention of dementia remains the main factor in reduction of dementia morbidity [9]. In perfect scenario, primary dementia prevention means postponing the onset of the disease [10]. Therefore, the most recent identification of the number of possibly modifiable and unmodifiable risk factors, associated with developing of dementia, could postpone the onset of the cognitive impairment. It was estimated that postponing the onset of dementia by 5 years on average, dementia morbidity could be decreased by 50.0% in total population [11].

More focus has recently been put on the health of medical workers. A number of studies [12, 13, 14] have been peformed to evaluate the use of psychoactive substances, stress in working environment and mental health of medical workers. However, little is known about prevalence of various preventable factors within medical community.

There are no studies about physical and mental health of medical workers in Lithuania. But the average age of practising medical workers in Lithuania in the recent years has reached 49 years with the trend to increase [15]. Due to the expanded requirements and expectations for medical competence and experience, this professional group should be aware of cognitively healthy aging. Thus the aim of our study was to estimate the risk of developing cognitive impairment/dementia among medical workers in Lithuania, as well as to assess the prevalence of factors possibly increasing and decreasing this risk.

MATERIALS AND METHODS

This study was approved by the Centre of Bioethics of the Lithuanian University of Health Sciences and its consent procedures on the 15th of January, 2016 (permission number: BEC-MF-199).

Study population

This cross-sectional study was conducted at three different medical institutions: one university hospital – Lithuanian University of Health Sciences Hospital Kaunas Clinics, one regional hospital – Kedainiai Hospital and one Primary Health Care Centre – in Kedainiai town. The inclusion criteria for the study were: medical worker – a doctor or a nurse; the consent to participate in the study and signed informed consent form; age – 50-years and older; no previous diagnosis of cognitive impairment.

In total, 200 medical workers were invited to participate in this study. At first, 30 questionnaires for pilot study were distributed. Validity of questionnaire was evaluted using Cronbach α criteria, equal 0.609. After that, the additional 170 questionnaires were distributed. One hundred and thirty eight questionnaires were returned and were suitable for final analysis (response rate – 69.0%).

Methods

An original questionnaire, based on literature review and selection of factors, increasing and decreasing the risk of cognitive impairment/dementia and items of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) scale was developed by the authors [16]. The questionnaire included information about sociodemographics (gender, age, education), height, weight, physical health (diabetes, arterial hipertension, etc), lifestyle factors (nutrition, smoking and alcohol consumption), cognitive and physical activity. During the data analysis, the risk factors were divided into two groups: six factors increasing the risk of developing cognitive impairment/dementia and four factors decreasing this risk.

Factors considered to increase the risk were: (1) obesity (body mass index (BMI) 30 kg/m² and higher [17, 18]; (2) arterial hypertension (AH), systolic blood pressure >140 mmHg [19, 20]; (3) type 2 diabetes (T2DM) [21, 22]; (4) currently active smoking (calculating smoking packs per years, according to the formula – (daily cigarete intake / 20) x duration of smoking in years) [23]; (5.1) problematic alcohol consumption, evaluated by as 14 and more standard units of alcohol (SUA) weekly [24, 25] and (5.2) alcohol non-users [26]; (6) family history of cognitive impairment within the first or the second-degree relatives [27].

Factors considered to decrease the risk were: (1) education lasted for 10 years or longer [24, 28]; (2) intensive cognitive activity: regular performing of 6 and more cognitive activities, 13 possibilities presented in the questionnaire (walking for pleasure or excursion, visiting friends or relatives, being visited by relatives or friends, physical conditioning, doing unpaid community volunteer work and etc) in the past year [29]; (3) regular physical activity in the past year [30, 31, 32]; (4) adherence to the Mediterranean diet, rated on "MedDiet" questionnaire score 7 or more [33, 34].

The estimated 20-year risk for medical workers to develop cognitive impairment/dementia was evaluated using the CAIDE scale, developed in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study [35]. The CAIDE scale is a validated tool for estimating 20-year dementia risk in the general population based on a midlife risk profile. Factors considered to increase and to decrease the risk of cognitive

impairment were evaluated according to the known odds ratios and the score (points) of each CAIDE item was calculated [24]. Future dementia most significantly is predicted by age (47–3 years – 3 points, ≥53 years – 4 points), education (7–9 years – 2 points, <6 years – 3 points), arterial hypertension (systolic blood pressure ≥140 mmHg – 2 points), obesity (body mass index ≥30 kg/m² – 2 points), low physical activity in the past year period (1 point), etc. The CAIDE total score is the sum of scores of all items (range 0–13). The CAIDE scale total score 0–5 shows the estimated 1.0% risk of dementia [95% CI 0.0–2.0]; a score 6–7 shows the risk of 1.9% [95% CI 0.2–3.5]; a score of 8–9 shows the risk of 4.2% [95% CI 1.9–6.4]; a score of 10–11 shows the risk of 7.4% [95% CI 4.1–10.6] and a score of 12–13 shows the risk of 16.4% [95% CI 9.7–23.1].

Statistical analysis

Sample size (n=172) was defined using Paniotto method, and was based on the number of 50 years and older of medical workers (n = 300) selected for this study and working in medical institutions. Data was analysed using Microsoft Office Excel 2007 and IMB SPSS Statistics 22.0 software. Statistical analysis included descriptive statistics, Cramér's V correlation coefficient, Chi-Square test of variable independence. Correlation coefficient and p value are given in results. Statistical significance was assumed at p≤0.05.

RESULTS

In total, 89.9% (n = 124) of study participants were females. Average age was 57.5 years (standard deviation (SD) 5.43); minimum age was 50, maximum – 80 years.

The distribution of the factors increasing the risk of developing cognitive impairment/dementia among medical workers is presented in Table 1. The lowest value of BMI in the sample was 17.5 kg/m², the highest – 34.6 kg/m². Based on BMI value, 8.7% of subjects were obese and were classified as a higher risk group. The vast majority did not indicate that they suffered from AH and T2DM. Thus, 37.0% of subjects with AH and 5.1% of subjects with T2DM were allocated to the higher risk group.

Only 10.1% of study subjects were active smokers and were allocated to the higher risk group. Based on evaluation by pack-years of smoking, all active smokers smoked up to 25 pack-years. In this sample, average number of pack-years of smoking was 9.3 (SD = 7.75). Additionally 12.3% were reported as ex-smokers, but that was not considered as a risk-increasing factor.

Among those who reported using alcohol, most frequent intake was once in a week (88.5%), none of the subjects indicated using alcohol more than three times per week. Most frequently, 13% of alcohol by volume (ABV) was used with 100 ml daily intake. Total average daily alcohol volume intake was 204.1 ml (SD = 237.40). Among those, who reported consuming alcohol, none was allocated to the higher risk group, because none reported using 14 or more SUAs per week (not problematic alcohol users). Otherwise, according to the data [26], not problematic alcohol use is associated with a lower risk for the development of dementia compared to alcohol non-users, therefore, more than a half (55.8%) of respondents in the study sample, who did not consume alcohol at all, were allocated to the higher risk group.

Table 1. **The distribution of factors increasing the risk of developing cognitive impairment/ dementia among medical workers (n=138)**

Risk factor			n (%)
Body mass index, kg/m²	<25.0		66 (47.8)
	25.0–29.9		60 (43.5)
	≥30.0		12 (8.7)
Arterial hypertension, systolic blood pressure mmHg	>140 mmHg		51 (37.0)
	≤140 mmHg		87 (63.0)
Type 2 diabetes	Yes		7 (5.1)
	No		131 (94.9)
Smoking	Yes, currently smoking		14 (10.1)
	Yes, smoked previously and quit		17 (12.3)
	No, never smoked		107 (77.5)
Alcohol consumption	Yes		61 (44.2)
	Days of weekly alcohol consumption	1	54 (88.5)
		2–3	7 (11.5)
	Alcohol by volume, %	5	7 (11.5)
		13	47 (77.0)
		40	7 (11.5)
	Alcohol volume intake, ml	100	40 (65.6)
		100–500	19 (31.1)
		>500	2 (3.2)
	Weekly SUA intake	<0	77 (55.8)
		0–14	61 (44.2)
		≥14	0 (0)
	No		77 (55.8)
Inheritance for dementia	1st degree relatives	Yes	48 (34.8)
	2nd degree relatives	Yes	43 (31.2)

SUA – standard unit of alcohol

More than one third of respondents were classified as the higher risk group according to family history of cognitive impairment in the first (34.2%) or the second-degree (31.2%) relatives.

The distribution of the sample according to the total number of risk-increasing factors is presented in Table 2. Only 8.7% of respondents in total sample did not have any factors increasing risk for cognitive impairment/ dementia; but also, only 1.4% – had all 6 risk factors. On average, subjects had 2.3 risk-increasing factors (SD = 1.10). Among those subjects with at least one risk factor identified, 61.3% – had no more than 2 risk factors, and 79.1% – no more than 3 factors. The most frequent risk factor was AH – separately or together with any other risk factor it was identified for 51 subjects (37.0%). The rearest risk factor was found to be T2DM – 7 cases (5.1%).

The distribution of the factors decreasing the risk of developing cognitive impairment/dementia among study

Table 2. **The distribution of sample of medical workers according to the total number of risk-increasing factors**

Total number of risk factors	n (%)
0	12 (8.7)
1	36 (26.1)
2	43 (31.2)
3	33 (23.9)
4	10 (7.2)
5	2 (1.4)
6	2 (1.4)

Table 3. **The distribution of factors decreasing the risk of developing cognitive impairment/ dementia among medical workers (n=138)**

Risk factor		n (%)
Regular physical activity in past year period	Yes	57 (41.3)
	No	81 (58.7)
Cognitive activity, sum of regular cognitive activities	≥6	96 (69.9)
	<6	42 (30.4)
Education, years	≥10	138 (100)
	<10	0 (0)
Adherence to Mediterranean diet, „MedDiet“ score	≥7	34(26.6)
	<7	104 (75.4)

participants is presented in Table 3. All subjects were found to have the same risk-decreasing factor – longer than 10-year duration of education. The second most frequent risk-decreasing factor was intensive cognitive activity after work – 69.9% of subjects were allocated to this group. Only 41.3% of respondents reported physically exercising on a regular basis during the past year period and only 26.6% of subjects adhered to the Mediterranean diet, which was the rearest risk-decreasing factor of cognitive impairment/dementia.

The distribution of the sample according to the total number of the risk-decreasing factors is presented in Table 4. Duration of education was excluded from further frequency analysis of the risk-decreasing factors, because all subjects were allocated to this risk-decreasing group. Any of the remaining three risk-decreasing factors were not indicated by 14.5% of subjects. The minority of the sample had all three additional risk-decreasing factors (7.2%). The biggest part (42.0%) of the sample was detected with one additional risk-decreasing factor. On average, subjects had additional 1.6 risk-decreasing factors (SD = 0.64). The most frequent additional risk-decreasing factor was cognitive activity (found in 70.0% of the sample, n = 96), the least frequent – adherence to the Mediterranean diet (34 cases, 25.0%).

The evaluation of the risk for medical workers to develop dementia in upcoming 20 years, according to the CAIDE scale and the distribution of the CAIDE scores are presented in Figure 1. None of subjects received total CAIDE score below 3 points – it could be explained by the fact that subjects were evaluated no less than 3 or 4 points due to their age (50 years and older); according to BMI, 12 subjects were assessed by 2 points; for physical inactivity, 81 subjects received 1 point; the value of systolic blood pressure (SBP) ≥140mmHg granted 2 points for 51 subjects. Generally, more than a half of subjects (55.1%) received 4 and 5 total CAIDE scores. Average sample CAIDE score was 5.3 points (SD = 1.43). Based on total scores, 1% risk of developing dementia in 20 years was determined for 85 subjects (61.6%), 1.9% risk – for 47 subjects (34.1%), and 4.2% risk – for 6 subjects (4.3%). None of the subjects was evaluated by 10 or more points of the CAIDE scale score, corresponding to 7.4% or higher risk of developing dementia.

Seeking to explore which risk factors contributed most to the total CAIDE scores, the frequency of higher CAIDE scores was evaluated for separate risk factors. The most frequent unmodifiable risk factor that contributed to higher total CAIDE score was age above 53 years; the most prevalent modifiable risk factor – absence of regular physical activity and non-adherence to the Mediterranean diet.

Evaluating the association between total CAIDE scores and scores of separate risk factors, it was found that the most frequent CAIDE scores by age were 5 (n = 33) and 4 (n = 30). Statistically significantly higher total CAIDE scores (Cramér's V coefficient 0.601, p<0.001) were determined in 53-year-old and older subjects. The most frequent CAIDE scores by systolic blood presure were also 4 and 5. Subjects with SBP

Table 4. **The distribution of sample of Lithuanian medical workers according to the total number of risk-decreasing factors**

Total number of risk factors	n (%)
0	20 (14.5)
1	58 (42.0)
2	50 (36.2)
3	10 (7.2)

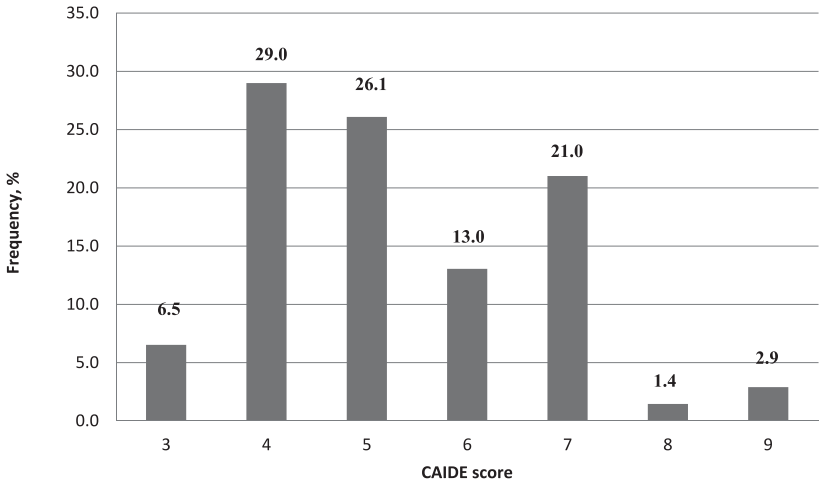

Figure 1. **Distribution of study sample by CAIDE total scores (%)**

≥140 mmHg had statistically significantly higher total CAIDE scores (Cramér's V coefficient 0.881, p<0.001). Checking the CAIDE scores according to BMI level, there were no cases scored 8 or 9 for BMI <30 kg/m². Similarly, there were no cases scored by 3, 4 or 5 points for BMI ≥30 kg/m². Subjects with BMI <30 kg/m² had statistically significantly lower total CAIDE scores (Cramér's V coefficient 0.723, p<0.001). The most frequent CAIDE scores by regular physical activity were 5 and 4 points. Statistically significantly higher total CAIDE scores were associated with absence of regular physical activity (Cramér's V coefficient 0.892, p<0.001; $\chi^2 = 107.022$, p<0.05).

DISCUSSION

The current study revealed that on average, a medical worker older than 50 years, has normal weight, has no AH or T2DM, never smoked before and does not currently smoke. Less than a half of medical workers are not problematic alcohol users – consumption of alcohol is 100 ml of 13% ABV alcohol once weekly in most cases. However, one third of medical workers had family history of cognitive impairment/dementia within the first or the second-degree relatives. The majority of study participants had no more than 3 risk-increasing factors for developing cognitive impairment/dementia. All subjects had the same dementia risk-decreasing factor – longer than 10 years duration of education. The vast majority were engaged in cognitive activity at their free time, however, respondents were physically inactive and poorly adhered to principles of the Mediterranean diet. Excluding long duration of education, 42.0% of subjects had one cognitive impairment/dementia risk-decreasing factor.

While there were no previous studies that evaluated the risk of developing cognitive impairment/ dementia among medical workers in Lithuania, the results of our study were compared to the national population data. The results of Statistical Health Study of Lithuanian Population in 2014 (SHSLP) were used for this comparison [36].

Overweight and obesity are more prevalent in total Lithuanian population compared to medical community (74.0–76.0% and 56.0% accordingly). The incidence of T2DM was also two times higher in general populiation in comparison to medical workers, 11.0% and 5.1% respectively. AH was found in 67.0% of Lithuanian population, and 5.1% of medical workers had AH in our study. According to our study, 41.3% of medical workers were physically active. This number is significantly lower in total population – only 7.0% of 55–74-year old population reported exercising regularly to strengthen their muscles.

The lower number of indicators of the interrelated factors (overweight, higher incidence of T2DM and AH, lower physical activity) in health workers compared to total Lithuanian population shows a positive attitude towards healthy lifestyle and prevention of chronic diseases.

This finding is also confirmed by statistics of alcohol consumption and smoking. Alcohol use was less prevalent in medical community than in national population of Lithuania (44.2% and 62.0–81.0% respectively). The prevalence of smoking among Lithuanian medical workers was 10.1%. Current smoking among these healthcare professionals, was lower than in general population (11.0–23.0%).

However, only 26.6% of medical workers followed the Mediterranean diet. Although consumption of fruit and vegetables is only one element of the Mediterranean diet, 50.0–59.0% of Lithuanian population of age group of 55–74 years had intake of recommended quantity of fruits and vegetables according to the SHSLP data. The issue of inadequate nutrition remains relevant in total population, as well as in medical community.

There are a small number of studies performed in other countries that evaluated the indicators of lifestyle and physical health in medical workers.

When compared the data related to obesity and metabolic syndrome with other researches, the results of our study are more encouraging. It is known that more than a half (64.0%) of Turkey hospital workers aged ≥50 years has abdominal obesity [37] in comparison to 8.7% in our study sample. According to Halgurd F. Ahmed and authors [38], 57.6% of healthcare providers in Iraque, older than 40 years, have metabolic syndrome.

According to the results of our study, only 41.3% of medical workers were physically active, but studies performed in other countries show even worse results. An Italian study found that only 26.1% of healthcare workers were not physical active. Also, the rates of physical inactivity are high not only among medical community, also in Italian general population [39].

A comparison of harmful habits among medical workers in other countries indicates that the prevalence of smoking is similar among general population and health care professionals in Lithuania and the US. According to Sharna L. and authors [40], healthcare professionals in the US had a smoking rate of 8.34%. vs 10.1% in our sample. However, the prevalence of alcohol consumption is higher in our medical workers (44.2%), compared to 71.3% of medical community of the Academic Hospital of Parma, Italy not consumming hard liquor at all [39]. It is possible that these indicators reflect the general trend for alcohol intake in Lithuania.

None in the medical workers sample was evaluated with less than 3 or more than 10 total CAIDE scores. Most often, the CAIDE score according to modifying factors, was increased by absence of regular physical activity. Subjects, who were evaluated with higher CAIDE scores (particularly older than 53 years, obese, physically inactive and with SBP higher than 140 mmHg), had statistically significantly higher risk of developing dementia in 20 years of lifetime. The defined risk of developing dementia in 20 years among medical workers was not higher than 4.2%. According to the control of dementia increasing risk factors, the medical workers could be a good example of healthy lifestyle practitioners in Lithuania. Otherwise, the data of study, which evaluated the risk of the occurrence of dementia in general population of Finland during the 20 years, show the similar risk of developing dementia in Lithuanian medical community (4.2% vs 4%, respectively) [16].

In this study, for the first time, Lithuanian medical workers were evaluated according to the development of the risk factors for cognitive impairment/dementia. This study helped not only to evaluate the incidence of midlife factors, but also to estimate the risk for medical workers to develop dementia in upcoming 20 years. However, our study has a few limitations. Definitely, the small sample size limited our ability to make more detailed evaluation of distribution of the risk factors, to compare them between urban and rural medical workers, men and women, perhaps even in specific professions. Considering future

research, the present study detected a trend, thus additional research is needed to precisely investigate the distribution of the risk factors among medical workers with a larger study sample. An ability to investigate serum cholesterol levels and apolipoprotein E genotype would be also beneficial.

In context of increasing duration of active participation in healthcare labour, as well as expanding requirements and expectations for medical competence and experience, it is extremely important for this professional group to be aware of the risk factors associated with increasing and decreasing the risks of developing cognitive impairment/dementia, and in this way maintaining functional cognitive capabilities.

CONCLUSIONS

1. Three-quarters of medical workers had no more than 3 risk-increasing factors for developing cognitive impairment/dementia, of which inheritance among the first-degree relatives was the most frequent.

2. The majority of medical workers had two cognitive impairment/dementia risk decreasing factors – long duration of education and intensive cognitive activity in free time.

3. Regardless of the fact that the risk of developing cognitive impairment/dementia in 20 years of lifetime among medical workers did not exceed 4.2%, the awareness and understanding of the main modifiable risk increasing factors – low physical inactivity and poor adherence to the principles of the Mediterranean diet- could reduce this risk even more.

Conflicts of interest
Authors declare no conflicts of interest.

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Associations of anxiety and depression with obstructive sleep apnea in middle age and elderly women with coronary artery disease

Nerimo, depresijos ir obstrukcinės miego apnėjos sąsajos tarp išemine širdies liga sergančių vidutinio ir vyresnio amžiaus moterų

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SUMMARY

Background. Women with obstructive sleep apnea (OSA) are considered as a separate group from men with OSA. Frequently, they present atypical symptoms, including anxiety and depression, therefore, are often underdiagnosed for OSA. Untreated OSA, as well as anxiety and depression, may contribute to poor coronary artery disease prognosis (CAD).

Aims. We aimed i) to investigate and compare a prevalence of depression and anxiety in OSA and no OSA patients, ii) to investigate the associations of anxiety and depression symptoms with OSA severity in middle age and elderly CAD female patients.

Materials and methods. In sum, 219 female CAD patients (mean age 61±7.7 years) attending a cardiac rehabilitation program participated in this cross-sectional study. All study patients underwent full night in-laboratory polysomnography. OSA severity was assessed with Apnea Hypopnea Index (AHI). Depression and anxiety symptoms were assessed with Hospital Anxiety and Depression Scale and Beck Depression Inventory-II for cognitive, affective and somatic symptoms of depression. Multiple multivariate regression analyses were performed to identify associations between anxiety or depression and OSA severity, independently from confounding factors such as NYHA functional class, arterial hypertension, age, body mass index, sociodemographic status (relationship, unemployment and education) and depression or anxiety.

Results. OSA was present in 29 % of study sample. Fifty three percent of study patients were positive for anxiety and 22 % of patients for depression symptoms. OSA patients did not differ on depression or anxiety symptoms when compared with non-OSA patients. AHI was not correlated with anxiety score or depression score. In contrast, subjective sleep quality was found to be correlated with depression (r=.499, p<.001) and anxiety score (r=.449, p<.001). OSA severity was not associated with anxiety, depression or somatic, affective and cognitive dimension of depression, independently from confounding factors.

Conclusions. In the sample of female CAD patients OSA is common but its severity is not associated with anxiety or depression, independently from confounding factors.

Keywords: obstructive sleep apnea, women, coronary artery disease, anxiety and depression, cognitive, affective and somatic symptoms of depression.

SANTRAUKA

Įvadas. Moterys, turinčios obstrukcinę miego apnėją (OMA), yra laikomos atskira grupe, lyginant su vyrais su OMA. Moterims dažnai būdingi atipiniai OMA simptomai, įskaitant nerimą ir depresiją, todėl dažnai OMA yra nediagnozuojama. Negydoma OMA, kaip ir negydomi nerimo bei depresijos simptomai, gali bloginti išeminės širdies ligos (IŠL) išeitis.

Tikslai. i) Įvertinti ir palyginti nerimo ir depresijos dažnį tarp OMA ir ne OMA pacientų, ii) įvertinti ryšį tarp nerimo/ depresijos simptomų ir OMA stiprumo tarp IŠL sergančių vidutinio ir vyresnio amžiaus moterų.

Tyrimo medžiaga ir metodai. Tyrimo imtį sudarė 219 IŠL sergančių moterų (amžiaus vidurkis 61±7,7 metai) dalyvaujančių kardiologinės reabilitacijos programoje. Visoms pacientėms atliktas laboratorinis visos nakties polisomnografijos tyrimas. OMA stiprumas vertintas Apnėjos hipoapnėjos indeksu (AHI). Depresijos ir nerimo simptomai vertini Ligoninės nerimo ir depresijos klausimynu, bei Beko depresijos klausimynu skirtu įvertini kognityvinę, afektinę ir somatinę depresijos dimensijas. Taikyta daugiamatė regresijos analizė skirta įvertinti ryšį tarp nerimo ar depresijos ir OMA stiprumo, nepriklausomai nuo kitų faktorių, tokių kaip NYHA funkcinė klasė, arterinė hipertenzija, amžius, kūno masės indeksas, sociodemografiniai faktoriai (santykiai, nedarbas, išsilavinimas) ir depresija ar nerimas.

Rezultatai. Tyrimo imtyje 29 proc. pacientų turėjo OMA. Penkiasdešimt trys procentai turėjo išreikštus nerimo ir 22 proc. depresijos simptomus. Nerimo ir depresijos buvimas nesiskyrė tarp moterų turinčių ir neturinčių OMA. AHI nekoreliavo su nerimo ir depresijos įverčiais. Tuo tarpu subjektyvus miego vertinimas buvo susijęs su nerimo (r=0,499; p<0,001) ir depresijos (r=0,449; p<0,001) įverčiais. OMA stiprumas nebuvo susijęs su nerimu ar depresija, ar kuria nors iš dep**resij**os dimensijų, nepriklausomai nuo kontroliuojamų faktorių.

Išvados. OMA yra paplitusi tarp IŠL moterų, tačiau jos stiprumas nėra susijęs su nerimo ar depresijos simptomais net ir kontroliuojant pagal kitus faktorius**.**

Raktažodžiai: obstrukcinė miego apnėja, moterys, išemine širdies liga, nerimas, depresija, kognityviniai, afektiniai ir somatiniai depresijos simptomai.

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INTRODUCTION

Obstructive sleep apnea (OSA), characterized by upper airway collapse resulting in repeated oxygen desaturation and sleep fragmentation [1], is associated with multiple deleterious physiological and psychological consequences [2]. OSA is recognized as independent risk factor for cardiovascular disease [3] and increased risk for cardiovascular mortality in both women and men [4]. OSA triggers multiple pathways such as increased sympathetic activity, oxidative stress and insulin resistance that may initiate or accelerate the underlying cardiovascular disease [5]. Although OSA could be modifiable cardiovascular factor, it is often underdiagnosed [6] thus placing CAD patients at disadvantage from recovering from cardiac event [7] and increasing risk for greater depression and anxiety symptoms, which in turn negatively affects CAD [8, 9].

Women with OSA are considered as a separate group from men with OSA. Literature suggests that frequency and severity of OSA is lower in female than men [10]. Moreover, women present female-specific clinical symptoms of OSA, such us depression, insomnia, morning headache, fatigue, mood disturbances [10, 11] and different comorbidities than men [12] thus are less likely to refer to sleep clinics for an evaluation for sleep briefing disorders [10, 12]. The Wisconsin sleep cohort study estimated that OSA was underdiagnosed in more than 90% of women with moderate to severe OSA [13]. The higher age among OSA female, lower OSA severity as well as frequency when compared with men could be explained by hormonal changes in menopause [14, 15]. Dancey and colleagues [16] in large study of 1,315 women found that OSA was twice as prevalent in postmenopausal women (>55 years) than premenopausal ones (<45 years) (47% vs 21%), even after controlling for body mass index (BMI) and neck circumference.

Frequently OSA female patients report "atypical" symptoms, such us insomnia, depression, nightmares, restless legs [17] and prior to OSA diagnosis are more likely to receive treatment with antipsychotics, anxiolytics and antidepressants [18], suggesting that women might experience anxiety and depression. There is still controversy in literature regarding relationship between anxiety and depression with OSA [19-21]. Khan and co-authors found that OSA was associated with higher levels of anxiety in CAD patients [22]. Longitudinal study of 2,818 OSA patients and 14,090 matched non-OSA participants showed that at 1-year follow-up incidence of depression was higher in OSA patients with 2.17 fold increased risk for depressive symptoms [21]. In contrast, no association between depression or anxiety with OSA were found in cross-sectional studies [23-25]. However, most of the studies were done in samples of men or together with women that could diminish differences among genders. For example, Lal with colleagues [26] in a study of early postmenopausal women (45-60 years) reported that women who were at high risk of OSA had more frequent depressive symptoms compared to women without OSA. In a cross-sectional study of 660 CAD male patients (43% were positive for OSA) it was found week but significant association between OSA severity measured by AHI with symptoms of depression [27]. Thus, we hypothesize that symptoms of depression and anxiety would be more prevalent in OSA female patients, as compared with non-OSA female patients, and associated with OSA severity. Most of the previous studies examined one dimension construct of depression in OSA patients [28] as well as in CAD patients [29]. However, there is some evidence that cognitive, affective and somatic dimensions of depression have been differently associated with cardiac morbidity and mortality [30]. One study examined two dimensions depression construct in OSA patients and showed that in contrast to men no relationship between apnea severity and depression was indicated in women [31].

The aim of the study was to examine association between anxiety and depression symptoms with OSA severity in CAD female patients, independently from previously established factors contributing to anxiety and depression such as cardiovascular condition, age, body mass index [9] and sociodemographic factors such as relationship status, employment and education [32].

MATERIAL AND METHODS

Participants and procedure

Consecutive female patients attending an in-patients cardiac rehabilitation program at the Behavioral Medicine Institute of the Lithuanian University of Health Sciences (Palanga, Lithuania) were invited to participate in this cross-sectional study during the period from 2007 September to 2016 October. In total 219 female age from 46 to 79 years participated in the study. All women were middle age or elderly and were considered "at risk" for menopause according literature [33, 14]. Within three days of admission to rehabilitation clinic all women were evaluated for sociodemographic characteristics, past and current diagnosis, traditional cardiac risk factors such as body mass index (BMI), smoking, history of diabetes mellitus, arterial hypertension. Cardiovascular functional status was assessed according to the New York Heart Association (NYHA) Functional Class [34]. All study patients were receiving standard treatment for secondary prevention of CAD according to the existing guidelines [35]. Women were excluded from the study if they had coronary artery bypass graft surgery, cognitive disorientation, communicative disabilities or other severe diseases, or did not speak Lithuanian fluently.

The study and its consent procedures were approved by Kaunas Regional Biomedical Research Ethics Committee, Kaunas, Lithuania. A written informed consent was obtained from each study patient.

Anxiety and depression symptoms

Anxiety and depression symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) [36]. The HADS is a self-rating 14 items scale consisting subscale of anxiety (HADS-A) and a subscale of depression (HADS-D) [36]. Possible total scores on both subscales range from 0 to 21 with higher scores indicating more severe symptoms. Scores on the HADS-A and HADS-D ≥8 indicate mild to severe symptoms of anxiety and depression and possible clinical depression and possible clinical anxiety, respectively. The Lithuanian version of the HADS has been shown to be reliable screening instrument for anxiety and depression symptoms in CAD patients [37] (Cronbach alphas for this study was .837 and .774, respectively). HADS reliability in OSA patients was also confirmed [38]. The Beck Depression Inventory – 2nd Edition (BDI-II) (shortened version) [39] was used for assessment of cognitive, affective and somatic dimensions of

depression. BDI-II questionnaire is a self-rating questionnaire measuring the severity of depressive symptoms on a scale from 0 to 3, where 0 indicates no symptoms and 3 indicates severe symptoms. The BDI-II was used for assessment of symptoms of depression: 6 BDI items were used to calculate cognitive symptoms, 3 items were used to calculate affective symptoms and 6 items were used to calculate somatic symptoms (Table 1). The BDI-II was utilized in OSA patients [31] and is valid and reliable instrument for assessment of depressive symptoms in Lithuanian CAD patients [40]. BDI-II subscales: cognitive (Cronbach alpha=.666), affective (Cronbach alpha=.501), somatic (Cronbach alpha=.622) showed acceptable internal consistency.

Subjective sleep quality

The Pittsburgh Sleep Quality Index (PSQI) is a seven domain (19 item) self-rated questionnaire evaluating subjective sleep quality during the last month. The seven domain scores of subjective sleep quality, sleep latency, sleep duration, sleep efficiency, daytime dysfunction, sleep fragmentation, and use of sleep aid medications combine to provide a global sleep quality index score. PSQI score range from 0 to 21, with greater than five indicating poor sleep quality. The possible scores range from 0–21, with greater than five indicative of impaired sleep quality[41]. Lithuanian version of PSQI [42] had good internal consistency Cronbach alphas for this study was .748).

Excessive daytime sleepiness

Epworth Sleepiness Scale (ESS) was used for assessment of daytime sleepiness [43]. The ESS consists from eight items. ESS score is ranging from 0 to 24. Every item could be rated from 0 (no chances of napping) to 3 (high chances of napping). Values >10 indicate significant sleepiness [44]. Interanl consistency was acceptable in this study (Cronbach alpha=.658).

Obstructive sleep apnea syndrome

Full-night in laboratory polysomnography (PSG) using Alice-4 model polysomnograph (Respironics) was used for assessment of severity of obstructive sleep apnea (OSA) syndrome. The sleep stages were scored according Rechtshaffen and Kales criteria [45]. Apnea/Hypopnea Index (AHI) was defined as the total number of apneas plus hypopneas per hour of sleep. A cessation of airflow for ≥10 s in the presence of out-of-phase thoraco-abdominal effort or as a fall in airflow for ≥10 s with out-of-phase thoraco-abdominal movement associated with a ≥4% fall in SaO2 was defined as OSA episode. OSA syndrome was diagnosed as present when the AHI was >5 AHI/hour: mild (5≥AHI<15), moderate OSA (15≥AHI<30) and severe OSA (AHI≥30) [1].

Statistical analysis

Before statistical analysis, normal distribution was evaluated. Differences between non-OSA and OSA groups were tested with Chi-square test and descriptive statistics were given as a percent (%) for group percentage comparison. Mann-Whitney U test was used when distribution was not normal, Descriptive statistics were given as median (minimum-maximum). In case of normal distribution T test was used and descriptive statistics were given as means ± standard deviation (SD). Spearman's correlation coefficients were calculated to access relationship between anxiety, depression, AHI, subjective sleep quality and excessive daytime sleepiness. Multiple multivariate regression analyses (Enter method) were performed to identify factors associated with anxiety and depression symptoms. The dependent variables were scores on HADS-D, HADS-A, BDI-II cognitive, BDI-II affective, BDI-II somatic scales. The independent variable was AHI with adjustment for potential confounding factors such as NYHA Functional Class, arterial hypertension, age, BMI, relationship status, employment, education, anxiety (while examine depression and its dimensions) and depression (while examine anxiety). A probability of .05 or less was used as a criterion to include an independent variable into multivariate model. The associations between the independent and dependent variables were expressed as standardized betas (β) and R^2 (goodness of fit of the models). All of the data was analyzed using SPSS (version 21.0; SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered to be statistically significant.

RESULTS

Sample characteristics

Women had an average age of 61±7.7 years, 97% of women were older than 55 years, 27% had university education, 37% were employed and 65% had a partner. An average of BMI was 31.6±5.7 (kg/m^2) in study sample. About 16% of patients had diabetes mellitus, about 12% were smoking and 63% had myocardial infarction. Twenty two of study patients had NYHA Functional Class III, 75% had arterial hypertension, 4% had history of stroke, 5% had chronic lung disease, 5% of patients used antidepressants and 25% of women used benzodiazepines. Seventy one percent of study patients complained on sleep quality and 7% reported daytime sleepiness.

Subjects with OSA represented 29% of study sample: 22% of patients had mild, 4% moderate and 2% severe OSA. Comparison analysis between non-OSA and OSA women revealed that OSA patients were older and had higher BMI (Table 2). Scores on AHI were significantly higher in OSA patients. Non-OSA and OSA patients did not differ on frequency of poor sleep quality (PSQI>5), daytime sleepiness (ESS>10),

Table 1. **Item content by Beck Depression Inventory-II dimensions [39]**

Cognitive	Affective	Somatic	Omitted items from 21 item BDI-II in the shortened model
2. Pessimism	4. Loss of pleasure	16. Change in sleep pattern	1. Sadness
3. Past failure	10. Crying	17. Irritability	5. Guilty feelings
6. Punishment feelings	12. Loss of interests	18. Change in appetite	7. Self-dislike
8. Self-Criticalness		20. Tiredness or fatigue	11. Agitation
9. Suicidal thoughts or wishes		21. Loss of interests in sex	13. Indecisiveness
14. Worthlessness			15. Loss of energy

Table 2. **Descriptives stratified by presence of obstructive sleep apnea (OSA) in coronary artery disease female patients**

Variable	All (n=219)	Non-OSA (n=156)	OSA (n=63)
	mean±SD, median (interquartile range) n (%)		
Sociodemographic factors			
Age	61.2±7.7	**60.5±7.9**	**63.0±6.9***
Education			
University	58(26.5)	44(28.2)	14(22.2)
College	34(15.5)	26(16.7)	8(12.7)
Professional secondary	50(22.8)	37(23.7)	13(20.6)
Secondary	56(25.6)	34(21.8)	22(34.9)
Not finished secondary	18(8.2)	12(7.7)	6(9.5)
Primary	3(1.4)	3(1.9)	0(0.0)
Employment			
Employed	82 (37.4)	63(40.4)	19(30.2)
Unemployed	137(62.6)	93(59.6)	44(69.8)
Relationship			
With partner	142(64.8)	105(67.3)	37(58.7)
Single	77(35.2)	51(32.7)	26(41.3)
Traditional cardiac risk factors			
Body mass index (kg/m^2)	31.6±5.7	**30.7±5.2**	**33.7±6.5*****
Smoking	27(12.3)	20(12.8)	7(11.1)
History of diabetes mellitus	34(15.5)	24(15.4)	10(15.9)
Clinical characteristics			
Myocardial infarction	138(63.0)	96(61.5)	42(66.7)
NYHA functional class			
I	5(2.3)	4(2.6)	1(1.6)
II	165(75.3)	122(78.2)	43(68.3)
III	49(22.4)	30(19.2)	19(30.2)
Arterial hypertension			
No	29(13.2)	25(16.0)	4(6.3)
High normal blood pressure	5(2.3)	3(1.9)	2(3.2)
I^o	9(4.1)	7(4.5)	2(3.2)
II^o	158(72.1)	108(69.2)	50(79.4)
III^o	18(8.2)	13(8.3)	5(7.9)
History of stroke	8(3.7)	6(3.8)	2(3.2)
Chronic lung diseases	10(4.6)	7(4.5)	3(4.8)
Use of antidepressant	10(4.6)	7(4.5)	3(4.8)
Benzodiazepines	55(25.1)	42(26.9)	13(20.6)
AHI score (events/hour)	2.3(0.95–5.9)	**1.5(0.6–2.6)**	**10.4(6.8–14.2)*****
Subjective sleep quality			
PSQI score >5	156(71.2)	111(71.2)	45(71.4)
ESS score >10	15(6.8)	8 (5.2)	7 (11.1)
Anxiety and depression			
HAD-A	8.0(5.0–11.0)	8.0(5.0–11.0)	8.0(4.0–10.0)
HAD-D	4.0(3.0–7.0)	4.0(3.0–7.0)	4.5(2.0–7.0)

OSA: Obstructive Sleep Apnea; NYHA: New York Heart Association; AHI: Apnea Hypopnea Index; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale.
Bold = group differences at
*p value < .05; **p value < .01; ***p value < .001

sociodemographic factors and clinical characteristics, anxiety and depression.

Anxiety, depression and OSA presence

Fifty three percent of study patients were positive for anxiety and 20% of patients for depression symptoms. No significant differences on prevalence of clinically significant symptoms of depression (19% vs 22%) or anxiety (54% vs 52%) between non-OSA and OSA groups were found. Comparison of scores on depression and anxiety between non-OSA and OSA patients revealed no statistical significant differences.

Anxiety, depression, OSA severity and subjective sleep quality

Spearman's correlation analysis showed that AHI was not associated with anxiety, depression or any depression dimension score (Table 3). ESS score was also not associated with anxiety or depression. Where as subjective sleep quality was positively associated with both, anxiety and depression symptoms, as well as cognitive, affective and somatic symptoms of depression.

Multiple regression analyses (Table 4) adjusted for AHI, NYHA functional class, arterial hypertension, age, BMI, relationship status, employment, education, anxiety or depression symptoms were carried to assess the contribution of these variables to the anxiety or depression. Results revealed that AHI was not associated with anxiety and depression as well as cognitive, affective, somatic domains of depression. Older age was associated with higher anxiety and depression scores and higher scores on somatic dimension of depression. Higher education was associated with higher scores on affective domain of depression. Anxiety symptoms contributed to higher scores on depression (all domains: cognitive, affective and somatic).

DISCUSSION

In this study we examined anxiety and depression symptoms, in sample of middle age and elderly CAD female patients in respect to OSA presence. Our results suggest that OSA female patients did not differ on anxiety or depression when compared with non-OSA patients and severity of OSA did not contribute to anxiety or depression when controlling for contributing factors.

In line with cross-sectional study of CAD patients results [7] we found 29% of CAD women positive for OSA in our sample. This number is higher than in general population reporting about 17 % of OSA in women [46]. OSA frequently coexists, but is usually being undiagnosed in CAD patients [47]. Systematic review and meta-analysis of the studies supports an association between OSA and CAD [48]. Moreover, recent study [15] showed that rate of OSA in postmenopausal women is higher than in premenopausal and rises with age. Thus, it was expected to indicate higher rates of OSA in our study sample of middle age and elder women meeting criteria for postmenopausal women [33].

Low number of OSA women reported sleepiness (7%) in our study, poor subjective sleep quality and sleepiness complains did not differ among non-OSA and OSA women, more than half were positive for anxiety and 22 % for depression. These symptoms are different from characteristic for OSA men reported in literature [46] and in line with literature suggests that CAD women with OSA may have distinct symptom profile than men [10].

Table 3. **Spearman correlations between OSA severity, anxiety, depression, dimensions of depression, subjective sleep quality and excessive daytime sleepiness**

	AHI	HADS-A	HADS-D	BDI-II cognitive	BDI-II affective	BDI-II somatic	PSQI	ESS
AHI	–	.004	.047	.013	-.082	.012	-.075	.125
HADS-A		–	**.626*** **	**.606*** **	**.544** **	**.584*** **	**.322*** **	.158
HADS-D			–	**.596*** **	**.593*** **	**.593*** **	**.447*** **	.110
BDI-II cognitive				–	**.572*** **	**.535*** **	**.450*** **	.072
BDI-II affective					–	**.539*** **	**.359*** **	.095
BDI-II somatic						–	**.359*** **	.129
PSQI							–	-.162
ESS								–

HADS-A: Hospital Anxiety and Depression scale, Anxiety subscale, HADS-D: Hospital Anxiety and Depression scale, Depression subscale; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale
Bold = group differences at *p value < .05; **p value < .01; ***p value < .001

We were particularly interested in association between AHI and anxiety and AHI and depression in CAD women because of the controversy regarding relationship between anxiety and depression symptoms with OSA [19, 28, 2]. We found higher rate of depressive and anxiety symptoms than it was found in cross-sectional study of healthy elderly women with OSA (anxiety 48 % and depression 12%) [24]. However we did not found differences between rates of anxiety and depression between non-OSA and OSA women. Higher rates of anxiety and depression also could be link not only with the presence of OSA but also with cardiac disease severity. A study comparing OSA in stable CAD patients with patients with refractory angina found that prevalence of depression symptoms was 15 % in stable CAD patients and more than four times higher in refractory angina patients [25].

Our findings demonstrated that there is no association between AHI and anxiety or depression in women. Our findings are in line with several cross-sectional studies [23, 31] indicating no relationship between AHI and self- reported anxiety and depression symptoms. In contrast, to our study results Sforza with colleagues [24] indicated that OSA women over 65 years were 5.44 times more likely to have depression. Such discrepancies among studies could be explained by the fact that in our study only 2 % of participants have severe and 4 % mild OSA. Most of the women have mild OSA which may not contribute to depression [28]. Presence of brain sites showing injury in OSA and depression independently, suggest that a portion of the damage found in OSA may be related to injuries associated with depressive symptoms [49].

Table 4. **Factors significantly associated with anxiety, depression, cognitive, affective and somatic depression symptoms evaluated by multiple regression analyzes**

	HADS-A	HADS-D	BDI-II cognitive	BDI-II affective	BDI-II somatic
			β (p)		
Apnea Hypopnea Index					
NYHA class					
Arterial hypertension					
Age (years)	**.105** **	**.209*** **			**.251*** **
Body mass index					
Single					
Unemployed					
Education				**.159** **	
HADS-A		**.639*** **	**.609*** **	**.540*** **	**.577*** **
HADS-D	**.636*** **				
R^2	.437	.434	0.402	0.372	0.438

HADS-A: Hospital Anxiety and Depression scale, Anxiety subscale, HADS-D: Hospital Anxiety and Depression scale, Depression subscale; Bold = group differences at *p value < .05; **p value < .01; ***p value < .001

Our proposed model (Table 4) suggests that not AHI but other factors, such us older age contributes to anxiety; and older age and higher education contributes to depression. In a study of 302 male patients with severe OSA was found that subjective sleep quality mediates relationship between symptoms of depression assessed with BDI and OSA severity measured with RDI [50]. It might be that subjective symptoms, including subjective sleep quality and anxiety, mediate relationship between depressive symptoms and objective measures of OSA severity. In our study we have found association between subjective sleep quality with anxiety and depression. Thus, future studies should address effect of subjective symptoms on relationship between depression and OSA in CAD patients.

The strengths of this study are objective evaluation of OSA by overnight in-laboratory polysomnography and well-validated tests for measuring anxiety and depression in CAD patients. Also, this study assessed different domains of depression, not only one dimensional construct of depression. Moreover, this study is notable for its ability to control for factors associated with anxiety and depression, including NYHA functional class, arterial hypertension, age, BMI and sociodemographic status (relationship, unemployment and education).

A cross-sectional design of the study is a major limitation, which prevented us from assessing a causal relationship between OSA and symptoms of anxiety or depression. OSA and depression have overlapping symptoms [28], thereby resulting in complex relationship which was not the primary aim of this study and were not evaluated. Objective measures of hormonal changes and data on menstrual symptoms were not collected in this study thus limiting accuracy for women categorization as postmenopausal. Moreover, our study results could be generalized only to stable middle age and elderly CAD female patients entering cardiac rehabilitation.

CONCLUSIONS

Results of study suggest that OSA, as well as symptoms of depression and anxiety are prevalent in CAD female patients. However OSA and non-OSA women do not differ on anxiety or depression. Severity of OSA did not contribute

to anxiety or neither dimension of depression, independently from confounding factors. Future studies should address effect of subjective symptoms on relationship between anxiety and depression and OSA in CAD patients,

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Does the Exposure Method Used in Cognitive Behavioural Therapy for Panic Disorder with Agoraphobia Affect Treatment Outcome?

Ar ekspozicijos metodika, naudojama taikant kognityvinę ir elgesio terapiją panikos sutrikimo su agorafobija gydymui, turi įtakos terapijos efektyvumui?

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SUMMARY

Panic disorder (PD) is characterized by the presence of recurrent unexpected panic attacks and persistent worrying about the occurrence of a new panic attack. 30 to 60 % of PD sufferers develop agoraphobia [PD(A)], a condition characterised by avoidance of anxiety-provoking situations, such as public transport, open or enclosed places or leaving the home alone. Cognitive Behavioral Therapy (CBT) is an effective psychological treatment for PD(A). One of its key components is exposure, a method for systematically approaching anxiety-provoking stimuli. However, up to 30% of PD(A) sufferers find traditional in vivo exposure (IVE) procedures too aversive. One way to increase the likelihood of sufferers engaging in exposure assignments is to carry them out in session. In addition, new exposure methods are being explored as alternatives to traditional IVE, such as virtual reality exposure. However, little is known about how treatment outcomes produced by these different exposure methods compare to one another.

Aim. To review relevant literature to find out whether the exposure method used affects treatment outcomes in CBT for PDA.

Method. A systematic search of the following databases was performed: CINAHL, PsychINFO, Cochrane Library, PsychArticles, Scopus, Medline, and Wed of Science. Inclusion and exclusion criteria were applied to the identified papers and the final set of studies was assessed according to methodological criteria.

Results. Eight papers were included in the review. Four papers were experimental studies comparing different modes of exposure, one paper was a retrospective naturalistic study, and three papers compared virtual reality exposure therapy (VRET)-enhanced CBT to traditional CBT. The methodological quality of the studies and the validity of their conclusions was found to be mixed.

Conclusions. The review concluded that different exposure methods tended to produce similar results. However, some indications of IVE being superior to virtual reality exposure (VRE) were found. Some findings also indicated that the combination of therapist-assisted and self-led exposure might be superior to self-led exposure only. However, studies in this area are low in numbers and of mixed quality, therfore, more high-quality research in needed.

SANTRAUKA

Įvadas. Panikos sutrikimas (PS) yra liga, kurios metu pacientai patiria stipraus nerimo (panikos) priepuolius, lydimus nuolatinio nerimavimo ir baimės, kad ištiks kitas priepuolis. Iki 60 proc. sergančiųjų patiria ir agorafobiją, t.y. baimę ir vengimą būti situacijose, provokuojančiose nerimą. Kognityvinė ir elgesio terapija (KET) yra efektyvus panikos sutrikimo su agorafobija (PSA) gydymo būdas, kurio vienas iš svarbiausių komponentų yra ekspozicija, t.y. laipsniško artėjimo prie nerimą provokuojančio stimulo metodika. Tačiau iki 30 proc. sergančiųjų PSA tradicinę ekspoziciją gyvai laiko atgrasia, todėl vienintelis būdas padidinti ekspozicijų tikimybę yra atlikti jas terapinių sesijų metu. Kita vertus, atsiranda ir kitų alternatyvų ekspozicijoms gyvai, pavyzdžiui, ekspozicija virtualioje realybėje, tačiau iki šiol mažai žinoma kokius terapinius rezultatus duoda skirtingi ekspozicijos metodai.

Tyrimo tikslas. Atlikus atitinkančią kriterijus mokslinių publikacijų apžvalgą, nustatyti ar paskelbtų mokslinių tyrimų duomenys leidžia spręsti apie skirtingų ekspozicijos metodikų efektyvumą gydant panikos sutrikimą su agorafobija.

Tyrimo metodai. Šioje literatūros apžvalgoje pateikiama sisteminio tyrimo, atlikto siekiant išsiaiškinti kokie terapijos rezultatai pasiekiami naudojant skirtingus ekspozicijos metodus, duomenys. Buvo nagrinėjamos 8 įtraukimo kriterijus atitinkančios mokslinės publikacijos. Keturios publikacijos pateikė eksperimentinius duomenis, lyginant skirtingus ekspozicijos metodus. Vienas nagrinėtas straipsnis buvo natūralistinė studija, o trys publikacijos pateikė tradicinės KET ir KET, naudojant virtualę realybę palyginimo rezultatus.

Rezultatai ir išvados. Apžvalgos rezultatai rodo, kad skirtingi ekspozicijos metodai vertinant bendrai duoda panašius terapijos rezultatus. Tačiau, buvo nustayta, kad esant specifinėms indikacijoms, ekspozicija gyvai gali būti efektyvesnė už virtualios realybės technikų taikymą, o su terapeutu daromos ekspozicijos derinimas su ekspozicija savarankiškai gali būti pranašesnis už ekspoziciją, atliekamą tik savarankiškai.

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INTRODUCTION

Definition of Panic Disorder

Panic disorder (PD) is a common psychiatric disorder primarily characterised by recurrent unexpected panic attacks [1]. Panic attack is defined as a sudden surge of strong fear or intense discomfort that is characterised by four or more of the following symptoms: palpitations; trembling or shaking; sweating; feelings of choking; sensations of shortness of breath; abdominal distress; chest pain or discomfort, feeling faint; numbness; chills or heat sensations; derealisation or depersonalisation; fear of losing control or "going crazy"; and fear of dying [1]. To meet the diagnostic criteria for PD, at least one of the attacks needs to be followed by a period of no less than one month of persistent worrying about the occurrence of a new panic attack and its consequences; and/or changes in individual's behaviour aimed at avoiding future panic attacks [1].

In the American tradition, panic attacks have been considered to be the primary pathological phenomenon and the core of the disorder, agoraphobia being an avoidance behavior secondary to it with DSM-IV considering agoraphobia a residual diagnosis [2]. From the European perspective, however, agoraphobia had always been seen as something that can occur with or without panic attacks [3]. Similarly, in DSM-V [1], panic disorder and agoraphobia are defined as two separate diagnoses.

Prevalence of Panic Disorder

European studies found that the 12-month prevalence of PD is 1.8% [2, 4]. In the United States, the lifetime prevalence of PD with or without agoraphobia is estimated to be approximately 4.7% [5].

PD rates are reported to be consistently higher among females than males [2]. The National Comorbidity Survey conducted in the USA between 1990 and 1992 showed that women were 2.5 more likely to suffer from PD than men [6]. A very recent study [7] (also found that women tended to report more severe subjective suffering than men despite similar severity symptoms as measured by an observer-rated scale.

Age of onset and typical course

The mean age of onset of PD is reported to be in the 20s [8], but both panic attacks and PD can also begin in childhood or early adolescence [3, 9]. The majority of all PD cases tend to report an onset before the age of 25 [2].

If untreated, panic disorder is usually chronic and recurrent. Wittchen et al. [10] reported that remission without treatment had been observed in 14% of cases during seven years.

Comorbidity

"Pure" PD appears to be rare; usually, it is highly comorbid with a range of other mental disorders and this pattern is consistent across available European community studies [2]. Significant associations have been found between PD and almost all anxiety, mood, substance misuse and somatoform disorders [2]. Most frequently, PD is comorbid with depressive disorders, followed by other anxiety disorders [2]. PD has also been found to be strongly associated with substance use disorders as well as somatoform disorders [11–13]. Comorbid agoraphobia is often associated with poorer treatment outcomes [14–16].

Incidence of PD co-morbid with agoraphobia has been reported to be between 35% and 65% [17]. To be diagnosed with agoraphobia, an individual must experience marked fear of and avoid two or more of the following situations: using public transportation, being in open or enclosed places, being outside of the home alone or being in a crowd or standing in line. Usually, the fear is persistent and lasts for six months or longer [1].

The 12-month prevalence of agoraphobia without PD in EU countries has been reported to be 1.3%, and the gender differences seem to be even larger than in PD, i.e. 3:1 [2]. The typical onset of Agoraphobia has also been reported to occur in the 20s, but slightly later than PD [2].

Existing treatments for Panic Disorder

Studies indicate that PD sufferers usually obtain mental health care from GPs [5]. However, half of the patients who see their GPs, are estimated not to receive anxiety- specific treatment [18]. According to some estimates, only 10% of European individuals suffering from panic disorder receive adequate treatments, i.e. pharmacological or CBT [2].

NICE guidelines in the UK [19] specify that individuals suffering from PD should be offered either a psychological treatment in the form of CBT, a pharmacological treatment by antidepressant medication or guided self-help.

An extensive meta-analysis [20] found that CBT is at least as effective as pharmacological treatments. Moreover, she also found that data on the efficacy of medication in the treatment of PD might be exaggerated by a publication bias, as studies that found non-significant results remained unpublished.

Although various treatments by antidepressant medication have been found to be effective, relapse rates following termination of these treatments are relatively high. A 15-year follow-up study of people originally treated for PD with alprazolam and imipramine, found that only 18% of the patients remained symptom free, while 51% of the patients still had anxiety attacks and received pharmacologic treatment, but appeared to have learned to cope with their anxiety symptoms and their daily functioning had improved [16]. Similar long-term outcomes have been reported in a 7-year follow-up study [21] which showed that most patients were doing well, despite the fact that some of their anxiety symptoms persisted.

A Swedish study [16] described changes in pharmacological treatment for PD in Sweden in the period between the late 1980s and 2003, as reflected in their study sample. At the end of the 1980s, 85% of the PD patients they studied continuously used benzodiazepines, in contrast to only 18% at 15-year follow-up in 2002; the opposite trend was observed in the use of antidepressants. However, Carpiniello et al. [22] reported that in the Italian PD patient cohort they had studied, 37% of patients taking drugs regularly at follow-up were on benzodiazepines, 20% were on antidepressants alone, while 43% were taking both benzodiazepines and antidepressants on a regular basis. In the UK, regular use of benzodiazepines is not recommended [19] due to their potentially damaging long-term effects, and the only recommended pharmacological interventions are either selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs).

Better long-term outcomes are believed to be one of the strengths of psychological therapies for PD. For example, Clark et al. [23] demonstrated that PD patients with no, mild or

moderate agoraphobia treated with CBT were significantly less likely to endorse catastrophic interpretation of bodily sensations than individuals treated by applied relaxation or imipramine; the study also demonstrated that the stronger individuals endorsed such beliefs, the more likely they were to relapse.

Gould et al. [24] concluded in their meta-analysis that cognitive-behavioural treatments consisting of cognitive restructuring and interoceptive exposure showed the strongest effect and that CBT produced on average better results than pharmacological or combination treatments. Furthermore, they found that the gains were very well maintained at follow-up on average one year later, while pharmacological treatment showed marked slippage of gains.

A recent meta-analysis of 124 studies [20] found that both CBT and BT were effective in alleviating anxiety symptoms when treating individuals with PD with agoraphobia. However, adding the cognitive element was found to be more effective for the associated depressive symptoms and CBT also had a smaller drop-out rate compared to BT (12.7% and 18.3% respectively). CBT was found to be at least as effective as pharmacological treatment, and no difference was found between CBT only and combination treatments, consisting of CBT and a pharmacological intervention [20].

CBT treatments for panic disorder

Currently, exposure based procedures and cognitive restructuring are considered to be the core elements in the treatment of PD; exposure-based techniques usually contain both interoceptive elements for treating panic and in vivo elements for agoraphobic symptoms [20]. Exposure therapy is defined as repeated approach toward fear-provoking stimuli and has been the dominant method used in CBT for anxiety disorders since the development of these treatments [25].

Sharp, Power, and Swanson [26] demonstrated that both individual and group CBT were equally effective for PD. CBT mainly targets the perpetuating factors of panic disorder and agoraphobia, which include avoidant behaviours and cognitive biases [27].

Butler et al. [28] concluded in their review of meta-analyses that outcomes for the effectiveness of CT for PD are robust. However, psychological treatments tend to achieve better results the shorter the time since the onset of the disorder [29]. CBT has been demonstrated to be efficacious for PD without agoraphobia and for PD with agoraphobia when agoraphobia is mild to moderate [30]. However, between 26% and 40% of PD patients do not benefit significantly from CBT [30-31]. Ramnerö & Öst [32] reported that PD patients with moderate to severe agoraphobia had poorer treatment outcomes in an in vivo exposure-based therapy programme; the magnitude of change at post-treatment and follow-up was also negatively predicted by agoraphobic severity.

Cognitive Model of Panic

Clark's [33] cognitive model of panic is derived from Beck's cognitive model of depression and suggests that panic attacks are the result of catastrophic misinterpretation of certain bodily sensations and that treatment should, therefore, focus on correction of these interpretations. Clark's [33] conceptualisation of panic acknowledges that biological factors may also play a role in panic attacks, especially by increasing individual's vulnerability to such attacks although, in this model, catastrophic interpretation of bodily sensations is considered to be a necessary condition for the production of a panic attack. Further studies have demonstrated that panic attacks are consistently associated with anticipated physical, mental, or behavioural catastrophes, e.g. death, heart attack, loss of control or going crazy [34].

Behaviour-oriented Approaches

In the United States a mainly exposure-based psychological treatment for PD was developed by Barlow et al. [35]. Although the two treatment packages contain both cognitive and behavioural components, Clark's model focuses primarily on the cognitive, while Barlow's model relies to a larger extent on the behavioural techniques [36]. Nearly three decades later these two approaches are considered to be the gold standard of CBT treatments for PD and have received strongest empirical support [29] and both emphasize the concept of learned fear of bodily sensations, particularly the ones associated with autonomic arousal [25].

Sánchez-Meca et al. [29] in their meta-analysis of psychological treatments for PD proposed a predictive model for differential efficacy of the specific techniques in CBT and found that exposure seems to be the critical component in CBT for panic disorder. The authors also reported that in vivo exposure seems to be significantly more effective than exposure in imagination.

Theoretical aspects of exposure-based Treatments

Modern exposure-based treatments for anxiety disorders derive from Wolpe's [37] systematic desensitization approach [38]. However, although these treatments have been actively used for a number of decades, the theoretical understanding of why and how exposure works was slower to develop; and as a good proportion, but not all patients benefit from these treatments, a better understanding of the mechanism governing exposure-based techniques can provide new insights into why some individuals fail to benefit from them [38].

One of the most influential theories aiming to explain the mechanisms behind exposure-based interventions is Foa and Kozak's [39] emotional processing theory. Foa and Kozak [39] suggested that in exposure-based treatments certain indicators can be used to measure whether appropriate processing of fear-related information is taking place, and these are emotional arousal during exposure trials, within-session habituation (WSH; defined as decrease in physiological reactivity and reported anxiety during repeated presentations of feared stimuli) and between-session habituation (BSH; defined as decrease in the initial fearful reactions to stimuli).

Based on this theory, it was believed that levels of fear throughout exposure therapy reflect the levels of learning and are therefore very important for the therapeutic outcome; however, further research has produced mixed results in this area [40]. Furthermore, although physiological arousal usually declines within an exposure period, Craske et al. [40] conclude there is not enough data to support the idea that such declines indicate learning or can predict long-term improvement. Similarly, the authors postulate that evidence for the importance of BSH is limited as well and that the amount by which fear declines within session does not predict overall improvement.

Craske et al. [40, 25] (propose an alternative model based on the Pavlovian conditioning. In this model, it is hypothesised

that therapeutic changes in exposure-based treatments happen through extinction and that inhibitory learning is central for the extinction to take place. Inhibitory learning is based on the notion that the original association between a conditional and unconditional stimulus (CS and US) is left intact while a new learning about the relationship between the US and CS takes place [41]. This also explains how fear can again be reactivated in a different context or just by the passage of time [40].

Craske et al. [40] argue that the data on WSH and BSH mirror the effects observed by Bjork & Bjork [42] when performance during instruction has been found unable to predict the actual level of learning. Tolerance of fear is currently believed to be more critical for the success of exposure therapy than the decrease in levels of fear [25, 40].

Craske et al. [25] hypothesize that deficits in inhibitory learning may not only contribute to poor response to treatment but also contribute to the development of the pathological fear or anxiety in the first place and so methods that can enhance inhibitory learning during exposure-based treatments can be very valuable [25]. Craske et al. [25] suggest that inhibitory learning may be enhanced by expectancy violation, deepened extinction [43-44], removal of safety signals as well as providing exposure in multiple contexts. The latter has been found to decrease the likelihood of fear renewal both in laboratory studies [45] and in a clinical study [46].

Affect labeling has also been shown to solidify inhibitory learning [25]. Linguistic processing has been shown to reduce activity in the amygdala and attenuate anxiety [47]. Craske et al. [25] report routinely asking their patients to describe their emotional states while engaging in exposure.

Deacon et al. [48] found that interoceptive exposure was more effective if it continued until the individuals believed that the aversive consequences were 5% or less likely to happen. An important component of exposure is also memory consolidation after the exposure trial, which is encouraged by asking the individual to judge what they learned from the non-occurrence of the feared event, this way, the inhibitory association is strengthened [49].

The modes of exposure

Goldstein and Chambles [50] conceptualised bodily sensations as conditioned anxiety-provoking stimuli in PD patients and postulated the need to confront these stimuli using interoceptive exposure (IE). Barlow and Craske [51] define IE as deliberate induction of bodily sensations through various exercises, including head shaking, spinning, running in place or breathing through a straw with the aim to new learning experiences that may lead to a reduction of anxiety. The efficacy of IE in the treatment of PD is well demonstrated [52].

The effectiveness of in vivo exposure (IVE), or situational exposure, for PD with agoraphobia, has also been well demonstrated [53, 20, 29]. However, about 30 % of the patients fail to benefit from IVE because they find the procedure too challenging and drop out of treatment prematurely [54].

Virtual reality exposure (VRE) has been found to be effective in specific phobias [55–56]. Its advantages are that unpredictable events can be prevented, and that specific features can be created to address specific fears of the patient [57]. It has been suggested that VRE could be seen as a new way of applying both IE and IVE and may be useful in cases when patients are too afraid to confront real situations [58].

THE AIM OF THIS REVIEW

Despite the fact that the efficacy of exposure-based interventions for PD is well established, the data on whether certain modes of exposure delivery lead to better outcomes are scarce and mixed [59]. For example, Williams & Falbo [60] reported mixed results on whether the presence of the therapist improves the outcomes of IVE. Schumacher et al. [61] reported that not only patients but also therapists experience elevated levels of stress during IVE.

On the other hand, both IE and IVE are clinically feasible techniques that most mental health practitioners can implement in their practice. Therefore, more consistent data on what is most likely to help this particular client group could be beneficial. This systematic review will attempt to answer the question whether application of certain modes of exposure is more likely to produce positive treatment outcomes in PD(A) patients.

METHOD

Initial search strategy

A search of electronic databases: CINAHL, Cochrane Library, PsycInfo, PsychArticles, Scopus, Medline and Web of Science was made using the search terms below:

1. “Panic“ and “Exposure”
2. “Panic disorder” and “Exposure”
3. “Exposure” or “Exposure-based” and “panic disorder” or “panic” not “social phobia” or “social anxiety disorder” not “PTSD”
4. “Panic disorder” and “agoraphobia” not “social phobia” not “PTSD” not “trauma”

The search period was limited to 1980–2016. 1980 was chosen as the start year because that year the diagnosis of PD was introduced in DSM-III [62].

The initial searches in the listed databases produced 1790 papers. Titles revealed that many of the papers were not relevant and were removed, reducing the number to 457. The abstracts of these were examined to determine their relevance. Based on the information provided in the abstracts 428 papers were removed, and 29 papers were retained for full-text examination.

Additional searches

Initial searches produced several meta-analyses and reviews on virtual reality exposure for anxiety disorders [63–65, 56, 66–67)]. References in these meta-analyses and reviews and the selected full-text papers were examined. Six published experts in the area were contacted by e-mail. These searches produced additional three papers. Full-text versions of these papers were obtained.

Inclusion and exclusion criteria

The obtained 32 full-text articles were evaluated based on the criteria described below. As the number of articles was limited, full texts papers were examined to ensure the relevance of the selected studies. The inclusion criteria were kept quite wide as studies examining different modes of exposure delivery are rather scarce. The inclusion criteria applied for papers in this systematic review were as follows:

- Written in English, German or Spanish
- Participants meet criteria for both PD and agoraphobia
- At least two different modes of exposure delivery are compared in the study

To reduce the bias that might occur if only studies written

in the English language are included, this systematic review also aimed to include studies published in English and Spanish.

Excluded papers

Twenty-four papers were excluded from this review after full-text examination. Reasons for exclusion are detailed in Figure 1.

RESULTS

This section summarizes the findings of the reviewed papers and the analyses of their methodological strengths and weaknesses.

The process of excluding the papers at each stage is presented in Fgure 1.

Eight papers met the inclusion criteria. Two compared the effectiveness of therapist-led and self-directed IVE [59, 68]. One compared self-directed IVE and self-directed IE [69]. Two compared VRE and EIV [57–58]. Three papers compared VRE-enhanced CBT to standard CBT [70–72].

Methodological Evaluation and main findings

The main methodological characteristics are presented in Table 1.

DISCUSSION

The aim of this systematic review is to evaluate currently available research data on the influence of exposure method used in CBT for PDA on treatment outcomes. This section will discuss the findings of this review. Theoretical and clinical implications of the findings will be discussed as well, followed by the limitations of this review and suggestions for future research.

Summary of findings

The papers included in this review compared two or more exposure methods in CBT treatments for PDA. Studies 1–3 and 5 experimentally compared two or three exposure methods, while study 4 compared the implementation of exposure methods retrospectively. Papers 6–8 compared

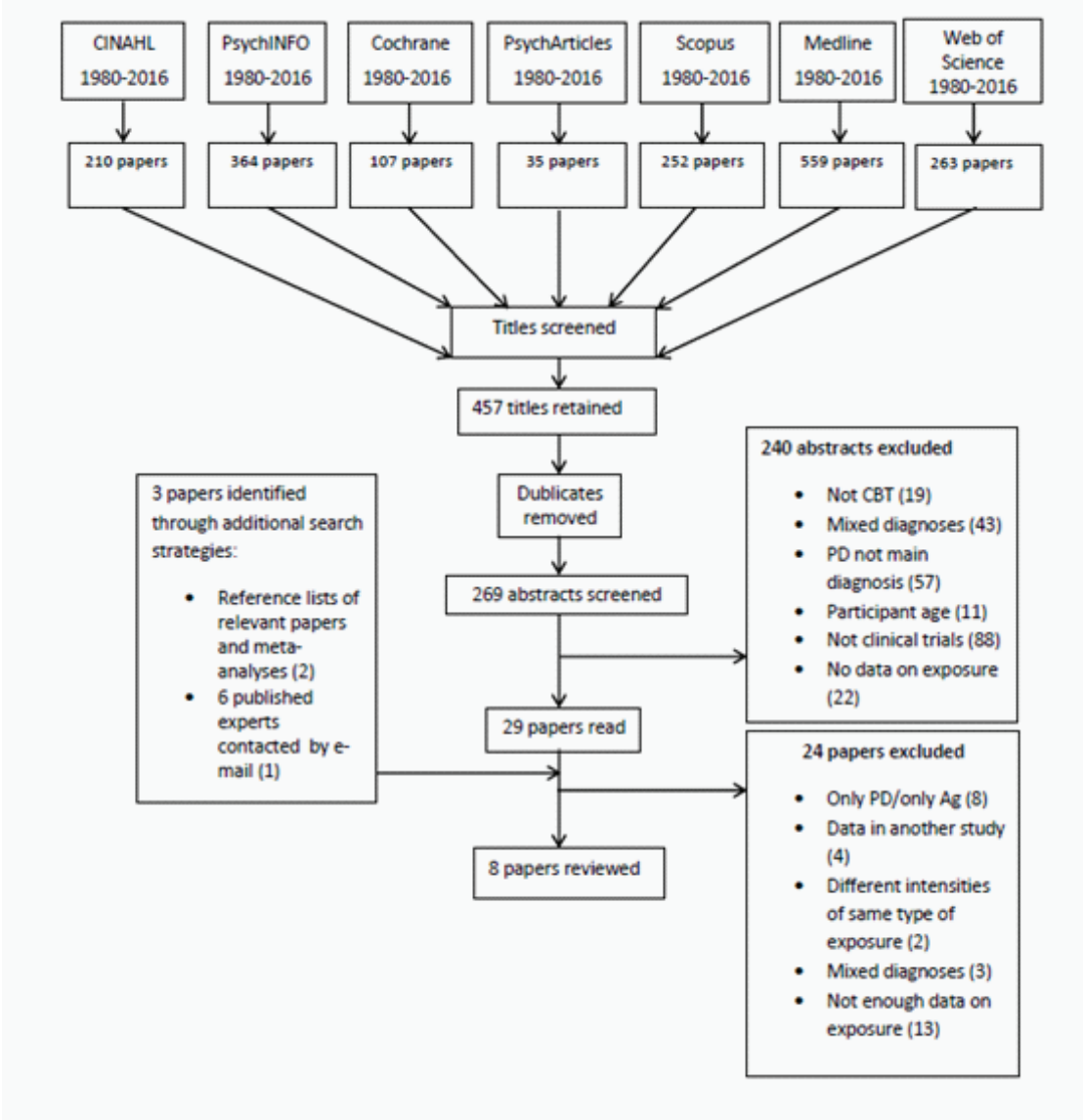

Figure 1. Flow chart showing the number of papers generated by each database search and the filtering process used to produce the final eight papers for review

Table 1. Main methodological characteristics of the reviewed studies

Study No.	Author/Year/Title/Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
1	Meyerbroeker K., Morina N., Kerkhof G.A., Emmelkamp P.M.G. 2013 Virtual Reality Exposure Does Not Provide Any Additional Value in Agoraphobic Patients: A Randomised Controlled Trial The Netherlands	To compare virtual reality exposure therapy (VRET) and exposure in vivo in terms of outcome and processes involved.	N=55 patients diagnosed with PD and severe Agoraphobia Two active conditions: 4 sessions of CBT+ either 6 sessions of VRET or 6 sessions of exposure in vivo Wait list control	32.6 % Almost equal dropout rate from both conditions	PDSS MI-alone BSQ ACQ Analysis by repeated measures ANOVA	ITT analysis: CBT+VRET and CBT+EIV superior to no treatment on: MI-alone F(1,44)=20.185, p=0.000 BSQ F(1,44)=13.468, p=0.001 ACQ F(1,44)=30.487, p=0.000 EIV had a stronger effect on panic disorder severity as measured by PDSS (F(2,40)=8.293, p=0.001) No significant difference between the active conditions on other measures	N/A	No follow-up data Relatively small sample size Substantial number of dropouts No data on self-exposure as homework
2	Botella C., Garcia-Palacios A., Villa H., Baños R.M., Quero S., Alcañiz M., Riva G. 2007 Virtual Reality Exposure in the Treatment of Panic Disorder and Agoraphobia: A Controlled Study Spain	To study the efficacy of virtual reality exposure in the treatment of panic disorder with or without agoraphobia	N=37 patients All diagnosed with panic disorder, 82.7% of the sample also diagnosed with agoraphobia Three experimental conditions: VRE, IVE and WL control. The active treatment composed of three modules: 1) education about anxiety and PDA, cognitive restructuring and breathing training (2 sessions) 2) Exposure (IVE or VRE; 6 sessions) 3) Relapse prevention (1 session)	No data	PA record PDSS ASI FQ-Ag BDI MS CGI Analysis by repeated measures ANOVA	VRE and IVE conditions did not differ in any outcome variable Patients in both active treatments improved significantly more than subjects in the WL condition on all outcome measures. Belief in catastrophic thought F(2,34)=8.29, p<0.001), PDSS F(2,34)=15.16, p<0.0001, MS global impairment F(2,33)=3.79, p<0.05 and CGI F=(2,33)=22.793, p<0.0001; FQ-agoraphobia F (2,33)=5.88, p<0.01; ASI F(2,34)=18.55, p<0.0001 100 % in IVE and 90.9% in VRE had achieved clinical improvement (free of panic or 50% reduction in panic frequency)	12-month follow-up Both treatments equally efficacious on all variables at follow-up (no significant time x condition interaction found) Further improvement on four outcome variables: belief in catastrophic thought F(1,22)=4.48, p<0.05), PDSS F(1,22)=15.94, p<0.001, MS global impairment F(1,21)=9.56, p<0.01 and CGI F=(1,22)=6.14, p<0.05. Gains maintained on all other measures. At follow-up, 90% of the participants in IVE condition and 91.6% in VRE condition met criteria for clinical improvement (free of panic or 50% reduction in panic frequency)	No data on dropouts Small sample size Not all the participants met criteria for both panic disorder and agoraphobia (17.1 % had been diagnosed with PD without agoraphobia). 66.6 % of the sample were taking medication for PD(A)

Table 1. Main methodological characteristics of the reviewed studies

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
3	Gloster A.T., Wittchen H.U., Einsle F., Helbig-Lang S., Hamm A.O., et al. 2011 Psychological Treatment for Panic Disorder With Agoraphobia: A Randomised Controlled Trial to Examine the Role of Therapist-Guided Exposure in Situ in CBT Follow up data in: Gloster A.T., Hauke Ch., Höfler M., Einsle F., Fydrich T., Hamm A., Sthröhle A., Wittchen H-U. 2013 Long-term stability of cognitive behavioral therapy effects for panic disorder with agoraphobia: A two-year follow-up study / Germany	To evaluate whether therapist-guided exposure in vivo is associated with more pervasive and long-lasting effects than therapist-prescribed exposure in vivo.	N=369 patients diagnosed with panic disorder and agoraphobia Multicenter randomised controlled trial with three experimental conditions: CBT T+, CBT T- and WL control CBT variants identical in content, structure and length, except for implementation of exposure in vivo The active treatment comprised: education, indvidualised behavioural analysis, rationale for exposure, interoceptive exposure, in vivo exposure In both active treatment conditions, participants were encouraged to engage in three exposure-related assignments each week, in T+ condition one assignment was led by the therapist, and two were self-led, in T- condition all assignments were self-led	19.6 % prior to post, additional 8.6% between post and 6 month follow-up No significant differences in attrition between T+ and T-	HAS CGI Number of panic attacks measured by PAS MI Statistical analysis: ITT Analysis by linear regressions (for dimensional variables) and cumulative logistic regressions (the categorical CGI variable) Effects tested for the second time adjusting for baseline variables, as a baseline difference on CGI was found between T+ and T- groups () Chi-square tests of independence and logistic regressions were used for binary outcomes (“yes”/”no”.)	Significant improvement on all outcome measures T+ improved more than T- on CGI (z=1.76, p=0.039) and MI (t_{335}=3.12, p=0.001) Reduction in agoraphobic avoidance accelerated after exposure was introduced Patients in T+ condition engaged in exposure assignments significantly more often and for longer in the last 24 hours prior to sessions 6–8 and 10–11; mean difference in frequency=0.64, t_{240}=5.87, p<0.001; mean difference in duration: 25.09 min, t_{240}= 3.19, p<0.001 A dose-response relationship for time X frequency of exposure and reduction in agoraphobic avoidance t_{212}= 2.32, p<0.011	*6 months follow-up:* Further improvement on all outcome measures, effect sizes ranging from 0.02 to 1.0 T+ improved further more than T- on Clinical Global Impression (z=1.76, p=0.039) and Mobility Inventory Greater reduction in panic attacks in T+ than T- (t_{299}= 1,69, p=0.047) Significant increase in number of participants reporting no panic attacks in T+ group (19,1%), but no further improvement in T- group (0.7%), t_{298}= 3.26, p<0.001 *24-month follow-up:* Effects sizes somewhat lower than at 6 month follow-up Most participants retained their status of responder/non-responder Agoraphobic avoidance lower in T+ group (d=0.37, p<0.05) The level of symptomatology as measured by effect size started to recede towards the post-treatment results. (Deterioration significant for HAM-A, MI and CGI, all p’s <0.05) T+ reported a significant worsening of symptoms between FU-6 and FU-24 on PAS and CGI (p’s <0.05. Patients in the T- condition reported worsening between FU-6 and FU-24 only on the MI (p<0.05). No significant difference between the proportion of patients who reported having sought additional treatment during the follow-up period: 35,9% in T+ condition and 38,6% in T- condition, $\chi^2(1)$=0.16, p=.693	Uneven sample sizes across the treatment groups: n=163 in T+ group, n=138 in T- group, n=68 in WL control group. Patients in T+ condition more frequently diagnosed with depression (49.5% vs. 37,0%, $\chi^2(1) = 4.03$, p=.045, more likely to report at least one panic attack in the previous week (79.8% vs. 68.2%, $\chi^2(1) = 5.3$, p=.021, and had higher global severity (CGI: M = 5.4, SD = 0.7 vs. M = 5.2, SD=0.7,z= -2.61, p=.009

Table 1. (Continued)

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
4	Klan T., Persike M., Hiller W. 2016 Effectiveness of Therapist-Guided exposure and Programmed Self-Exposure in the Outpatient Treatment of Panic Disorder with Agoraphobia / Germany	To examine the frequency and effectiveness of therapist-guided exposure and planned self-exposure in cognitive behavioural therapy for PDA in a university outpatient clinic.	Case series N=93 patients diagnosed with PDA Anxiety symptoms assessed before and after treatment	N/A	The German version of: MI ACQ BSQ Analysis by: Kruskal-Wallis H-Test Welch-corrected t-tests	IE modality did not have a significant effect on *agoraphobic avoidance* Significant difference in decrease in *agoraphobic avoidance b*etween a) combined IE and only therapist-led IE [$t(60) = -2.12$, $p<0.05$] b) No IE and combined IE [$t(49) = -2.20$, $p<0.05$] No significant effect of IE modality on *anxious cognitions* (ACQ) No significant effect of IE modality on f*ear of bodily sensations* (BSQ) IVE: significant effect of this exposure modality on *agoraphobic avoidance* after removing 4 outliers from the sample, [(χ^2 (2, N = 85)=6.44, $p<0.05$] Significant difference in effects on *agoraphobic avoidance* between "No IVE" and "Combined IVE": [$t(71) = -3.06$, $p<0.1$] Significant difference in effects on *agoraphobic avoidance* between "Combined IVE" and "Patient-led IVE" after removing 4 outliers from the sample: [$t(71) = -2.12$, $p<0.05$] No significant difference in *agoraphobic avoidance* between "No IV" and "Patient-led IVE" Significant effect of IVE modality on change in ACQ scores: [(χ^2 (2, N =8 9) =6 .02, $p<0.05$] Significant differences in change in ACQ scores between conditions "Combined IVE" and "No IVE" after removing the 4 outliers: [$t(68) = -4.06$, $p<0.01$] No significant effect of IVE modality on changes in fear of bodily sensations (BSQ)	No data	Non-experimental design

Table 1. (Continued)

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
5	Ito L.M., De Arujo L.A., Tess V.L.C., De Barros-Neto T.P., Asbahr F.R., Marks I. 2001 Self-exposure therapy for panic disorder with agoraphobia / Brasil	To compare the effects of a) in vivo, b) interoceptive and c) combined in vivo and interoceptive exposure in the treatment of panic disorder and agoraphobia	N=80 outpatients randomised to one of the three forms of self-exposure (in vivo, IVE; interoceptive, IE; or combined, IVE+IE) or to a W/L control group Each treatment comprised seven sessions delivered over 10 weeks. All participants in active treatment groups received education about panic/agoraphobia and exposure, and two 45-minute sessions of therapist-assisted exposure. Participants were asked to carry out 60 minutes of daily exposure homework. At the end of treatment all participants were asked to continue doing corresponding homework assignments during follow-up and to keep a diary of this to week 62 (1-year follow-up). Both interoceptive exposure groups were trained in slow deep breathing	12%	Two phobic targets, for avoidance and fear (each score range 0–16) Four social adjustment targets (each score range 0–8) FQ ACQ Diary of panic frequency over 2 weeks BDI HAS CGI Analysis by: MANOVA (ITT) to compare the four treatment groups on main outcome measures χ^2 tests for non-parametric data and ANOVA for parametric data to compare clinical and demographic features at baseline	The three self-exposure treatments reduced panic and agoraphobia equally well. All of them improved significantly ($p<0.001$) on all 10 measures, and the improvement was significantly larger than in the control group ($p<0.001$) . The differences between the active conditions were non-significant on all measures. On phobic target avoidance the effect sizes were: d=2.5 for IVE group, d=3 for IE group and d=1.6 for IVE+IE group Patients who dropped out between week 0 and 10 were considered non-successes. Completers who improved by at least 30% on CGI scale at week 10 were rated as success. The three treatment conditions did not differ significantly on χ^2 tests regarding drop-out and success/non-success rates to week 10 or 62. Results The three groups did not differ significantly at post-treatment on responder rate. (The response criterion was a 50% or more decrease in the FQ agoraphobia sub-score between baseline and post-treatment.) Responder rates were: 45.8% in the CBT group, 42.1% in the VRET group and 35% in the WL condition. No significant differences between the active conditions on any measure.	Participants in all the active conditions kept their gains and improved further. The three self-exposure groups did not differ significantly from one another on the main outcome measures. For groups IVE, IE and IVE+IE, effects sizes increased on phobic target avoidance, CGI and HAS.	Most patients (69%) self-referred after reading an article in the lay press. 8 participants received booster sessions but this was not considered in the follow-up statistical analysis.

Table 1. (Continued)

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
6	Pelissolo A., Zaoui M., Aguayo G., Nan Yao S., Roche S. et al. 2012 Virtual Reality Exposure Therapy Versus Cognitive Behavior Therapy for Panic Disorder with Agoraphobia: A Randomised Comparison Study /France and Luxembourg	To compare the effects of VRET, CBT and a WL control condition in patients with panic disorder with agoraphobia	N=92 outpatients diagnosed with PDA. Patients randomised into three groups: VRET, CBT or WL control group. Both active treatments comprised 12 one-hour sessions In the VRET group, patients received purely VRE sessions based on individually designed exposure hierarchies and using 12 available virtual environments. They were also encouraged to practice exposure in real life situations but were not given formal structured exposure homework. In CBT group, the following methods were used: individualised functional analysis, relaxation training (advised to practice relaxation for 10 min daily), provoked hyperventilation and cognitive restructuring (symptom reattribution), eliciting catastrophic automatic thoughts, prolonged exposure in imagination, graded exposure in vivo tasks, structured exposure homework.	27.2 % The rates were equal in VRET and CBT groups, 22.7% and 23.2% respectively	FQ PDSS ACQ PPGAS STAI HAS BDI GAF SDS DES WSA ERS Analysis by: Fisher's exact test; Two-level hierarchic models: logistic regression with random intercepts; Kruskall-Wallis test	The three groups did not differ significantly at post-treatment on responder rate. (The response criterion was a 50% or more decrease in the FQ agoraphobia sub-score between baseline and post-treatment.) Responder rates were: 45.8% in the CBT group, 42.1% in the VRET group and 35% in the WL condition. No significant differences between the active conditions on any measure.	*6-month:* CBT group had significantly lower scores on Disturbance subscale of FQ and Phobia 1 subscale of PPGAS. No other significant differences were found between the groups. The responder rates increased to 44% in VRET group and 56.7% in CBT group. *12-month:* No significant differences between the two active groups on any measures. Responder rates increased further to 47.6% in the VRET group and 60.7% in the CBT group.	No outcome data on control group at post No attempts to control or measure levels of self-directed exposure in the VRET group
7	Vincelli F., Anolli L., Bouchard S., Wiederhold B. K., Bcia M. B. A., Zurloni V., Riva G. 2003 Experiential Cognitive Therapy in the Treatment of Panic Disorder with Agoraphobia: A Controlled Study /Italy	To compare the effectiveness of Experiential Cognitive Therapy (ECT, comprising elements of classical CBT and VR exposure) to standard CBT and WL control	N=12 female patients diagnosed with panic disorder and agoraphobia The patients were randomly assigned to one of three conditions: ECT, CBT or WL control. In the ECT group patients received 8 therapy sessions comprising education, monitoring of panic attacks, in vivo and interoceptive exposure, VRE, cognitive restructuring, relapse prevention, three booster sessions at 1, 3, and 6 months after treatment In the CBT group patients received 12 sessions in accordance with the protocol described by Rapee & Barlow (1991) comprising cognitive restructuring, interoceptive exposure and imaginary exposure.	0	BDI-II STAI ACQ FQ Analysis by: Wilcoxon-Mann-Whitney Test Wilcoxon Signed Ranks Test Kruskal-Wallis test	Both ECT and CBT groups improved significantly on all measures (All p values <0.05 on Wilcoxon Signed Rank Test comparing pre and post values of the outcome measures.)	Unavailable	U, χ^2 and W values and effect sizes not reported No data on ACQ scores provided Small sample size No follow-up data Criteria for clinically significant improvement poorly defined. Unclear for how long the patients had been panic free when measured at post-treatment

Table 1. (Continued)

Study No.	Author/Year/Title/ Country	Aim	Design	Attrition rate	Outcome Measures & Statistical Analyses	Results	Follow-up results	Methodological weaknesses
8	Choi. Y-H.,Vincelli F., Riva G., Wiederhold B. K., Lee J-H., Park K-H. 2005 Effects of Group Experimental Cognitive Therapy for the Treatment of Panic Disorder with Agoraphobia / South Korea	To compare the effectiveness of brief ExCT (4 sessions) containing VRE component to 12 –session panic control programme (PCP; Barlow & Craske, 1994) for the treatment of PDA	N=40 patients diagnosed with PDA. The patients were randomly assigned to one of two conditions: 4 sessions of ExCT or 12 sessions of PCP	No data provided	BDI STAI ASI PBQ ACQ BSQ Analysis by t-tests	Both groups improved statistically significantly on all measures PCP group improved significantly more on PBQ at post: [t(40) = –2.17, p<0.05] Improvement on other measures did not differ significantly between conditions	6-month follow-up A significant difference (χ^2=8.47, p<0.05) in numbers of participants who had stopped medication (benzodiazepines) at follow-up (12 participants in PCP group and 4 participants in ExCT group).	No WL control group naddressed differences in numbers of participants free from medication diazepines) at baseline (40 % in ExCT group and 15% in the PCP group).

Key for abbreviations for measures used:

ACQ	Anxious Cognitions Questionnaire [73]
ASI	Anxiety Sensitivity Index [74]
BDI	Beck Depression Inventory [75]
BSQ	Body Sensations Questionnaire [73]
CGI	Clinical Global Impression [76]
DES	Dissociative Experience Scale [77]
ERS	Expectancies Rating Scale [78]
FQ	Fear Questionnaire [79]
FQ-Ag	Fear Questionnaire, Agoraphobia Subscale [79]
GAF	Global Assessment of Functioning [80]
HAS	Hamilton Anxiety Rating Scale [81]
MS	Maladjustment Scale [82]
MI	Mobility Inventory [83]
PAS	Panic and Agoraphobia Scale [84]
PBQ	Panic Belief Questionnaire [85]
PDSS	Panic Disorder Severity Scale [86]
PPGAS	Panic, Phobia and Generalised Anxiety Scale [87]
SDS	Sheehan Disability Scale [88]
STAI	State and Trait Anxiety Questionnaire [89]
WSA	Work and Social Adjustment Scale [90]

VRET-enhanced CBT to standard CBT for PDA.

In general, the reviewed papers found relatively few significant differences between the results produced by different exposure methods. A more detailed summary of the findings is provided below.

Studies 1 and 2 experimentally compared two CBT treatment protocols, one comprising VRE and another one comprising traditional IVE. In both studies these were also compared to a WL control group. Study 1 found that both active treatments produced equal results at post-treatment on all PDA-specific measures (MI-alone, ACQ and BCQ), except PDSS, on which the in IVE group did significantly better, $F(2,40) = 8.293$, $p<0.001$.

Study 2 found no significant differences between the two active conditions on any outcome measures at post-treatment or 12-month follow-up. Between post-treatment and follow-up, participants in both active groups improved further on ACQ, $F(1,22) = 4.48$, $p<0.05$; PDSS, $F(1,22) = 15.94$, $p<0.001$; MS global impairment, $F(1,21) = 9.56$, $p<0.01$; and CGI $F(1,22) = 6.14$, $p<0.05$. Participants in both active groups maintained gains on all the other measures.

Study 3 compared two CBT treatment protocols, one combining in vivo therapist-led and self-led exposure and another one employing in vivo self-led exposure only. This study found that at post-treatment patients in both active conditions had improved significantly more than WL control group on all measures, but patients in the T+ condition improved more on MI (t_{335}= 3.12, p=0.01) and CGI (z = 1.76, p=0.039). At post-treatment, there were significantly more people in the T- group reporting no panic attacks in the previous week, than in the T+ group (47.2% vs. 58.0%), $\chi^2(1) = 3.45$, p=0.032, but the difference was not significant when controlling for baseline values. Furthermore, at 6-month follow-up, T+ group had continued to improve significantly (19.1% increase in participants with no panic attacks in the past week), while the T- group had not (0.7%), t_{298}= 3.26, $p<0.001$. At 24-month follow-up, the T+ groups did significantly better than T- group

on agoraphobic avoidance (MI: difference in d=0.37), p<0.05). The percentage of patients who had achieved clinically significant change in panic and agoraphobia symptoms as measured by the PAS did not differ between the T+ and T- groups at FU-24. Neither T+ nor T- achieved further improvements on any measures between FU-6 and FU-24. Although both groups were able to maintain gains, the T+ group reported a significant worsening of symptoms on PAS (d=–0.34, p=0.019) and CGI (d=–0.66, p=0.006), whereas patients in T- condition reported worsening on MI (d=–0.21, p=0.03).

Study 4 found that patients who engaged in both therapist-led and self-directed IVE, achieved greater reduction in agoraphobic avoidance as measured by MI, than those who did not engage in IVE at all, t(71)=–3.06, p<0.01, or who engaged in self-led IVE only, t(71)=–2.11, p<0.05. Combined IVE was also associated with greater improvement on ACQ than no IVE, t(68)=–4.06, p<0.01. However, no differences in improvement on BSQ were identified. Combined therapist-led and patient-led IE was found to be associated with greater reduction of MI scores than no IE, t(49)=–2.20, p<0.05. Combined IE was also more effective than only therapist-led IE in reducing MI scores: t(60)=–2.12, p<0.05

Study 5 compared three different types of self-led exposure: interoceptive, in vivo, and combined. This study found that participants in all three groups did equally well on all outcome measures (ACQ, CGI, HAS, FQ, FQAg, BDI). There were no significant differences between the active treatment groups at post-treatment, or at 6-month and 12-month follow-up. Between post-treatment and 12-month follow-up patients in all three active treatment groups continued to improve on CGI and HAS.

Studies 6, 7 and 8 looked at how VR exposure-based therapy compares to standard CBT. Study 6 found that both interventions produced equal results. However, this study failed to find statistically significant difference between the outcomes produced by the active treatment conditions and the WL control group at post-treatment, and 6-month and 12-month follow-up. At post-treatment, 45.8% of the sample in the CBT group, 42.1% in the VRET group and 35% in the WL control group met criteria for significant improvement (50% or larger reduction on the FQ-Ag). This study found that CBT group had improved significantly more than VRET group at 6-month follow-up on Disturbance Subscale of FQ and Phobia 1 Subscale of PPGAS.

Study 7 found that 12 sessions of CBT and 8 sessions of VRET produced equal results on FQ. Furthermore, participants in both groups reported no panic attacks at post-treatment.

Study 8 compared standard 12-week CBT programme for PDA to 4 sessions of experiential cognitive therapy (ExCT) comprising standard CBT techniques and VR exposure. This study found that at post-treatment participants in both active conditions were doing equally well. However, at 6-month follow-up significantly more participants in the CBT group than in the ExCT group were no longer taking anxiolytic medication to manage their PDA (χ^2=8.47, p<0.05).

In summary, although in most cases different exposure methods produced similar results in the reviewed studies, some significant differences were uncovered. On several occasions, VRET was outperformed by more classical exposure methods. In study 1, IVE produced better outcomes than VRET on PDSS; in study 6, CBT comprising IE, exposure in imagination and structured self-exposure homework outperformed VRET on FQ and PPGAS at follow-up; in study 8, PCP comprising IVE did better than VRET-enhanced ExCT on PBQ at post and on number of participants who discontinued anxiolytic medication at 6-month follow-up.

In addition, combination of therapist-led and self-led IVE was found to be superior to self-led exposure in studies 3 and 4. Participants in the therapist-assisted group in study 3 achieved better results on MI and CGI at post-treatment, and on HAS at 6-months follow-up. Similarly, study 4 found that combined (therapist-led and self-led) IE was superior to therapist-led IE only, while combined IVE was superior to self-led IVE only.

Implications for clinical practice and theory development

The reviewed studies generally report positive outcomes and large effect sizes, supporting the notion that CBT treatments comprising exposure techniques are efficacious in treatment of PDA. However, several authors have pointed out that exposure is not routinely used in clinical practice despite of the solid evidence supporting the safety and effectiveness of these methods [91-93]. This is also mirrored in the reviewed studies, with experimental studies having allocated a considerably larger proportion of the therapy time to exposure assignments than the retrospective naturalistic study.

IVE has accumulated a strong evidence base as key treatment ingredient for PDA, including positive outcomes at long-term follow-up (up to 14 years) [94, 95]. The efficacy of IVE, which sometimes exceeded that of other modalities, was further demonstrated in the reviewed studies.

VRE has been demonstrated to produce promising outcomes in treatment of specific phobias [96-97]. The reviewed studies found that VRE can produce almost equally good results in PDA patients as IVE, both short- and longer-term. Furthermore, VRE was shown to be effective for severely impaired patients. However, the hopes that VRE could be a more acceptable alternative than IVE, which up to 30% of patients find too aversive [54], have not been confirmed in the reviewed studies. Page [98] criticised the research on VRET in anxiety disorders for small sample sizes. This was also the case in the reviewed studies. Therefore, the findings need to be to interpreted with caution and more research is indicated.

The findings in the reviewed studies indicated that therapist-assisted and self-led exposure produced almost equal outcomes, with therapist-assisted exposure being slightly superior in reducing agoraphobic avoidance. This is a promising finding in the context of low-intensity CBT, which can be delivered online or over the phone, and implies that the therapist is not able to participate in exposure assignments. At the same time, the findings suggest that whenever possible, incorporating therapist-assisted exposure in session might be beneficial, especially for reduction of agoraphobic avoidance, which has been demonstrated to predict long-term stability of treatment gains [99].

Furthermore, participants in most reviewed studies engaged in several types of exposure across the conditions, which again might have contributed to the positive outcomes through the consolidation of learning in various contexts [25].

The evidence from the reviewed studies further support the effectiveness of exposure-based techniques for PDA. The

reviewed studies were conducted in seven different countries yet produced similar results, suggesting the universality of CBT based treatments. Similar conclusions were drawn by Kenardy et al. [100] in a study investigating the effectiveness of standard CBT for PD in Scotland and Australia. This study concluded that "treatment effectiveness is robust to cultural difference" (p. 1074).

Summary of the methodological evaluation

The reviewed studies varied in their methodological quality. While studies 1 and 3 succeeded to control for most extraneous variables and compared two otherwise identical treatment packages where the only difference was the exposure method, the rest of the studies had some serious methodological problems. Study 2 did not provide any data on attrition and failed to report whether participants were encouraged to engage in exposure homework. Study 4 was a retrospective study, so it is not possible to draw any conclusions on causal effects of the interventions, as no extraneous variables had been controlled. In study 5 which studied effects of self-led exposure, all the participants received two sessions of therapist-led exposure first. This might have affected the patients' ability to engage in self-led exposure later in treatment. In study 6, participants in the VRET condition were encouraged to regularly engage in self-led in vivo exposure between sessions, making it difficult to separate between the effects of VRET and self-led IVE. Similarly, in Study 7, participants who received VRET, were encouraged to engage in graded self-exposure between sessions, and each session started with the review of the homework. In contrast, participants in the CBT condition in this study did not receive in vivo exposure in sessions and the study did not provide any data on what kind of homework participants in this condition were asked to do.

In study 8, the ExCT condition, which included VRE exposure, consisted of 4 sessions only, in contrast to the CBT condition which comprised 12 sessions. As the two conditions differed so greatly in the length of intervention, it is difficult to establish whether the relative poorer long-term outcomes in the ExCT group were the result of the specific components of the intervention, or its inadequate length. Furthermore, participants in ExCT condition underwent both IE and IVE in session, again making it difficult to distinguish between the effects of VRET and other types of exposure.

Sample sizes in the studies were also very different. Study 3 was the biggest study and had 369 participants, while study 7 had only 12. None of the studies provided a priori sample size calculations.

In addition to that, the samples in the studies varied considerably in complexity. While studies 1, 5 and 7 excluded patients with the comorbid MDD, 37.7% of the patients in study 3 and 17% of the patients in study 4 were diagnosed with comorbid depression at baseline. Roy Byrne et al. [101] found that people with comorbid lifetime major depression reported a larger number of physiological symptoms during their panic attacks and that both current and lifetime depression-panic comorbidity was associated with more severe, persistent and disabling illness.

In summary, criticisms of the reviewed studies include small sample sizes and possible lack of statistical power, scarcity of long-term follow-up data and limited control of confounding variables.

Overall the findings of this systematic review demonstrate that various exposure-based methods produce positive and similar short-term and longer-term outcomes, although IVE, especially when administered both in session and as homework, may produce superior outcomes. However, these results should be interpreted with caution, as identified methodological weaknesses in a number of the reviewed studies make it difficult to draw robust conclusions. Further high-quality research is clearly needed.

Limitations of this review

When interpreting the findings of this systematic review it is important to take its limitations into account. The quality of search has a crucial effect on the validity of the results of a systematic review [102]. Attempts were made to identify relevant papers by searching a high variety of databases and examining the reference lists of papers and meta-analyses. However, there is always a risk of papers being missed. In addition, although this review aimed to include papers published in English, German and Spanish, the search was performed only in the international databases predominantly containing English language papers. Therefore, German or Spanish papers could still have been missed. Furthermore, there may be some relevant research published in other languages that was not addressed.

The studies were identified and reviewed only by the author, leading to potential risk for subjectivity. Furthermore, all the included papers were published in peer-reviewed journals, which are more likely to publish papers reporting promising treatment effects [102].

Suggestions for future research

Future research should aim to study long-term outcomes produced by various exposure methods. More high-quality research is needed to establish the effectiveness of virtual reality exposure in the treatment of PDA. Only one reviewed study reported how much time participants spent engaging in exposure. The question of how much exposure is needed to produce satisfactory outcomes could also be addressed in future research. Furthermore, non-responders remain an important issue. One way of addressing this challenge could be to look at whether individuals who do not respond to a particular method of exposure would respond to exposure exercises delivered through a different modality.

CONCLUSION

Although CBT is the psychological treatment of choice for PDA, and exposure is an integral component of most CBT for PDA protocols, surprisingly few studies have looked little at how different modalities of exposure delivery compare to one another.

Although the currently available data suggests that different exposure modalities tend to produce similar results, there are some indications of IVE possibly producing somewhat superior outcomes to VRE and exposure delivered both in session and as homework leading to a larger reduction in agoraphobic avoidance than only self-led exposure. However, due to very small number of studies and a number of methodological issues in particular regarding non-inferiority trials, more high-quality research with larger samples is clearly needed.

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