Journal of Psychiatric Research 110 (2019) 152–158

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Childhood adversities, negative life events and outcomes of non-pharmacological treatments for depression in primary care: A secondary analysis of a randomized controlled trial

Diego Yacaman-Mendez[a,*], Mats Hallgren[b], Yvonne Forsell[a]

[a] Unit of Epidemiology and Public Health Intervention Research (EPHIR), Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden
[b] Unit of Epidemiology of Psychiatric Conditions, Substance Use and Social Environment (EPiCS), Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden

ARTICLE INFO

Keywords:
Depressive disorder
Non-pharmacological treatment
Treatment outcome
Primary care
Childhood adversities
Recent life events

ABSTRACT

Non-pharmacological treatments for depression are effective and available in primary care, but useful prognostic factors are lacking. Childhood adversities (CA) and negative recent life events (RLE) increase the risk and severity of depression, though their effect on treatment outcomes remains understudied. Using a sample of 737 adult participants of a multicenter randomized controlled trial receiving physical exercise, internet based cognitive-behavioral therapy or treatment as usual, alone or in combination with antidepressants, this prospective study aimed to determine the impact of CA, RLE and their interaction as predictors of outcomes of non-pharmacological treatments for mild-moderate depression in primary care. Outcomes were depression severity (MADRS score) and response to treatment (≥50% reduction in MADRS score) after three months. Linear regression and modified Poisson regression were used, interaction was assessed with a product term (CA*RLE) and epidemiological measures of interaction. The number of CA and RLE were associated with higher depression severity at follow-up (CA: β = 0.79, 95% CI: 0.14 to 1.44 and RLE: β = 0.52, 95% CI: 0.14 to 0.72) and showed a trend towards lower rates of response to treatment (RR = 0.94, 95% CI: 0.86 to 1.03; and RLE: RR = 0.95, 95% CI: 0.90 to 0.99). Interaction between CA and RLE was not significant for depression severity (β = 0.10, 95% CI: −2.12 to 0.41) nor for response to treatment (RERI = −0.05, 95% CI = −0.33 to 0.24). CA and RLE are associated with worse outcomes of non-pharmacological treatments in primary care. Further studies to identify predictors of outcomes of non-pharmaological treatments for depression are needed.

1. Introduction

The global burden of depressive disorders has increased steadily during the past decades, and it is expected to continue rising (G.B.D. DALYs and HALE Collaborators, 2017). Early identification and treatment of depression disorders can potentially reduce the severity of the disease and help to stop the progression to more severe forms, such as Mayor Depressive Disorders, and increase quality of life (Davidson et al., 2015; Forsell, 2007). However, dissemintaion of programs attempting to increase detection and treatment methods in primary care have not been successful (Kessler et al., 2003), and early diagnosis and treatment of depressive disorders remains challenging, especially in primary care settings were most patients first seek care (Tylee and Gandhi, 2005).

The most commonly used treatments for depressive disorders in primary care are antidepressants and psychological interventions such as cognitive behavioral therapy (CBT), which often require the involvement of specialized providers and are not readily available (Linde et al., 2015a, 2015b).

Recently, non-pharmacological treatment options such as internet or community based psychosocial interventions, self-help programs or physical exercise programs have shown to be useful for treatment of mild to moderate depression (Hallgren et al., 2015, 2016; Singla et al., 2017; Stubbs et al., 2018). Clinical guidelines globally now recommend early intervention with non-pharmacological options, alone or in combination with antidepressants, for the treatment of mild to moderate depression in primary care (National Institute for Health and Care Excellence, 2009; Socialstyrelsen, 2016; Zimmerman, 2018).

Several factors have been associated with outcomes of conventional treatment for depression, these include biological, clinical and social characteristics such as: age, sex, baseline severity, episode duration, psychiatric or somatic comorbidities, personality traits, and perceived

* Corresponding author. Department of Public Health Sciences, Karolinska Institutet, Stockholm, SE-171 77, Sweden.
E-mail addresses: diego.yacaman.mendez@ki.se (D. Yacaman-Mendez), Mats.Hallgren@ki.se (M. Hallgren), Yvonne.Forsell@ki.se (Y. Forsell).

https://doi.org/10.1016/j.jpsychires.2019.01.004
Received 1 August 2018; Received in revised form 19 December 2018; Accepted 3 January 2019

stress (Falola et al., 2017; Papakostas and Fava, 2008). However, there is a need for more information regarding factors influencing outcomes of non-pharmacological treatment options. Potential moderators of response to physical activity interventions for depression have been identified in a recent review (Schuch et al., 2016). Still, to our knowledge, no previous studies have assessed the roll of childhood adversities and negative life events on the outcomes of non-pharmacological treatment options.

The association between Childhood adversities (CA) and negative recent life events (RLE) with incidence of depression has been widely studied (Bellis et al., 2014; Horesh et al., 2008; Kendler et al., 1998; Kessler et al., 1997, 2010; Tiet et al., 2001). Usually, the effects of CA and RLE have been studied separately (Bock et al., 2009; Klein Daniel et al., 2009; You and Conner, 2009), and most studies have focused on major depressive disorder (MDD) (Gaynes et al., 2008) or on pharmacological and specialized interventions (Bock et al., 2009; Brown et al., 2010; Jain et al., 2013; Keers et al., 2010; Korkeila et al., 2010; Mazure et al., 2000; McLaughlin et al., 2010). Furthermore, results have been contrasting, with some studies suggesting a better response to treatment among those exposed to negative RLE (Keers et al., 2010) while others found them to be a risk factor for lower treatment response rates (Brown et al., 2010).

In this study, we examine the effect of CA, negative RLE and their interaction as predictors of response to non-pharmacological treatment in a sample of adults with mild-to-moderate depression treated in primary care.

2. Material and methods

2.1. Study population

This study is a secondary analysis of data from the REGASSA study: a multicenter, single-blinded and pragmatic Randomized Controlled Trial (RCT) exploring the effectiveness of Internet-based cognitive therapy (ICBT) and physical exercise (PE) in the treatment of mild-to-moderate depression compared to treatment as usual (TAU) in primary health-care. The study was carried out between February 2011 and March 2013 in six Swedish county councils (Stockholm, Skåne, Västra Götland, Kronoberg, Blekinge and Västmanland).

Swedish-speaking patients over 18 years of age who scored ≥9 points on the nine-item version of the Patient Health Questionnaire (PHQ-9) (Manea et al., 2012) were invited to participate by their primary care physician. Exclusion criteria included severe somatic illness, a primary alcohol or drug use disorder or psychiatric diagnoses that required specialist treatment (Hallgren et al., 2015).

After initial screening, a research nurse assessed eligibility, provided a detailed explanation of the study, obtained signed consent and performed the baseline assessment, which included standardized diagnostic questionnaires such as The Mini International Neuropsychiatric Interview (MINI), the Alcohol Use Disorders Identification Tests (AUDIT), as well as information about clinical and sociodemographic characteristics, including exposure to CA and negative RLE. After the baseline evaluation, an external and independent organization, The Karolinska Trial Alliance, performed the randomization using individuals as the unit of randomization and participants were allocated to receive ICBT, PE or TAU for 12 weeks.

A detailed description of the study procedure for each of the interventions has been published previously (Hallgren et al., 2016). In short, participants randomized to TAU received standard treatment for depression decided and administrated by their primary care physician. This consisted mostly on face to face counselling with a self-help or CBT focus lasting around 1 h. Participants received, in average, 8.2 sessions during the trial's intervention period. For 25% of the participants randomized to TAU, no intervention of any kind was recorded.

Those in the PE group were further randomized to one of three exercise programs (light, moderate or vigorous intensity) delivered by a licensed physical trainer in a modern fitness center with national presence in Sweden. All programs were designed to fulfill the recommended physical activity levels. Participants were asked to attend to three 60-min sessions a week for 12 weeks and completed an average of 12 out of the 36 sessions (33.3%).

Participants randomized to the ICBT group received treatment through a secure website operated by the county council. A short initial telephone call was done by a licensed psychologist to every participant to provide the basic information to use the ICBT service. Initially, basic modules targeted common depressive and work-related problems. Then, patient specific modules were individualized to provide self-help material for depression and work-related problems. Patient's responses as well as adherence were monitored weekly by a clinical psychologist, individuals considered at high-risk received extra support as needed. The complete treatment consisted of 13 modules, of which participants finished an average of 7.8 (60%).

Results of the REGASSA trial show a significant reduction in depressive symptoms in all groups after three months of intervention, and that these effects were still significant during the 12-month follow-up. The effect size of PE (mean difference 2.99, 95%CI 1.61 to 4.37) and ICBT (mean difference 2.83 95%CI 1.47 to 4.19) were significantly higher than the TAU group. (Hallgren et al., 2015, 2016; Helgadottir et al., 2017).

For the current prospective study, the three treatment arms of the original study were combined and used as “Treatment in Primary Care”, with a longitudinal design (baseline and 3 months post-treatment).

2.2. Variables

2.2.1. Outcome variables: depression severity and response to treatment

The primary study outcome was depression severity measured with the mean Montgomery-Åsberg Depression Rating Scale (MADRS) score after three months of intervention. The secondary outcome was response to treatment, defined as a reduction of ≥50% on the MADRS after 3-months, a cut-off point that is considered clinically useful and widely used in previous studies (Riedel et al., 2010).

2.2.2. Exposure variables

2.2.2.1. Childhood adversities. Exposure to CA was self-reported during the baseline evaluation, and included: 1) parental separation, 2) parental loss, 3) serious long-term emotional conflicts in the family, and 4) serious long-term financial difficulties; all occurring before 18 years of age and assessed retrospectively.

Three questions were used, the first one was: “which of the following best describes your upbringing?” with the following four response alternatives: a) My parents were together during my entire upbringing, b) My parents were never together during my upbringing, c) My parents divorced or moved away; and d) One or both of my parents died. This question was used to gather information regarding parental separation (option c) and parental loss (option d).

The two remaining questions evaluated the presence of serious emotional conflicts in the family and serious long-term financial difficulties: “did your family have financial problems during your upbringing?” and “did you experienced serious emotional difficulties in your family while growing up?”. The response alternatives were: a) No, not at all, b) Yes, mild and/or for a short period and c) Yes, serious and/or for a long period. These questions were dichotomized if emotional difficulties or financial problems were serious and/or present for a long period of time (option c).

The added number of CA experienced served as a continuous exposure variable and used in the regression models (Melas et al., 2018). For calculating the epidemiological measures of interaction, a dichotomous variable for exposure to CA was defined as present if at least one of the three events during childhood was reported.

2.2.2.2. Recent stressful life events. Exposure to negative RLE was

assessed with a self-reported checklist based in the Social Readjustment Rating Scale proposed by Holmes and Rahe (1967). The 22-item checklist was administered during the baseline evaluation. Examples of items include: serious interpersonal conflicts, serious disease, death of someone close, serious problems at work, etc. Participants were asked to indicate whether any of these events had occurred during the previous 12-months. Reliability and validity of the check-list has been previously reported (Dohrenwend Bruce et al., 2006; Rahe et al., 1974; Theorell, 2012) and previous studies in Swedish populations have used similar check-lists (Lundin et al., 2017; Melas et al., 2018; Möller et al., 2005).

The total number of negative RLE reported was positively skewed, with few participants reporting more than five negative RLE. Therefore, this variable is categorized as none, one, two, three, four and five or more RLE. Similar to previous studies (Brown et al., 2010; Keers et al., 2010). A binary variable was also defined as the occurrence of less than three, and three or more negative RLE and used to calculate the epidemiological measures of interaction.

2.2.3. Covariates

Covariates included in the models were selected based on previous knowledge and availability of the information collected for the REGASSA trial. Selection of covariates was done independently for exposure to CA and negative RLE. (Carter et al., 2012; Jain et al., 2013; Trivedi et al., 2006).

Risk and protective factors of response to treatment of depression have been widely studied and include several clinical, psychological, social and biological characteristics. However, these moderators seem to differ between pharmacological or psychosocial interventions, and show contrasting results between studies (Carter et al., 2012; Donker et al., 2013; Schuch et al., 2016; Tunvirachaisakul et al., 2018). Some of the factors more consistently mentioned across studies are age, sex, baseline severity of depression, depressive episode duration and somatic comorbidities.

Reports show that among others, sex, socioeconomic status and having parents with mental health disorders and recurrent depression increase the risk of suffering from childhood adversities, and also that having childhood adversities is associated with more recurrent depressive episodes of depression (Kessler et al., 2010). While Risk factors commonly associated with the occurrence of stressful life events during adulthood include socioeconomic position, personality factors, previous experience of CA, recurrent depressive episodes, a longer duration of depression, severity at the time of diagnosis and chronic somatic comorbidities (You and Conner, 2009).

In this analysis, to study the impact of CA as a predictor of non-pharmacological treatment outcomes, the covariates considered were age, sex and level of education to account for socioeconomic status and sex differences; and family history of mental health disorders and past depressive episodes. While the covariates included to study the impact of RLE were sex, previous CA, level of education, family history of mental health disorders, past depressive episodes and number of somatic comorbidities, and use of antidepressant medications.

Age was measured as a continuous variable at the time of enrolment. Sex categories were male and female. Level of education was initially distributed across four different categories and dichotomized based on tertiary education (above versus below). The occurrence of previous depressive episodes was assessed using the MINI questionnaire and dichotomized. Family history of mental health problems was evaluated with a question identifying the family member who suffered from adverse mental health, but not the specific diagnoses. This information was collapsed into a dichotomous variable: family history of mental health problems (present or absent). Physical comorbidities were self-reported using a list of 13 somatic disorders (e.g. cardiovascular disease, metabolic disease, neurological diseases, etc.) from which participants were asked to identify if they currently, or had previously, visited a physician because of any listed disorder. The number of reported comorbidities was used as a continuous variable.

2.3. Statistical analysis

Baseline social, clinical and demographical characteristics of the participants in each intervention arm were compared using Chi^2 for categorical variables and ANOVA for categorical data.

For the analysis of the main outcome, the severity of depressive symptoms at baseline and after three months of treatment were evaluated using multiple linear regression. The secondary outcome, response to treatment was assessed using modified Poisson regression with robust error variance (Zou, 2004). In both cases, separate analyses were performed for CA, RLE and for the effect of their interaction.

The interaction between CA and RLE on the primary outcome was evaluated by adding an interaction term, estimated as the product of childhood adversity and negative recent life events (CA*RLE) in the linear regression model. Complementary, for the Poisson regression model used for the secondary outcome, epidemiological measures of interaction (Relative Excess Risk due to Interaction (RERI) and the Attributable Proportion due to interaction (AP)) were calculated in order to assess the interaction while using a multiplicative model such as Poisson regression (Andersson et al., 2005).

Results from the multiple linear regression models are reported with non-standardized regression coefficients (β), p-values and 95% confidence intervals (CIs). Those from the modified Poisson regression models report estimated risk ratios (RR), p-values and 95% CIs. All statistical tests were performed using two-sided p-values and a 95% confidence level with STATA 15 (Statacorp, 2017).

2.4. Ethical considerations

All trial procedures were carried out in accordance with the ethical standards of the Helsinki Declaration for research involving human participants. Written informed consent was obtained from all participants.

The REGASSA study was approved by the Ethical Review Board of Stockholm County (Study ID: KT20110063) and is registered in the German Clinical Trials register (DRKS00008745).

3. Results

3.1. Participant characteristics and unadjusted associations

Of the 945 participants originally included in the REGASSA study, 737 (78%) participated in the post treatment examination (Hallgren et al., 2016). Missing values of any of the covariates used for this analysis was below 5%. Therefore, no imputation of data was performed. The mean age of the participants was 43.28 years (SD:12.27), and those over 60 years old represented 10.18% of the study sample. Baseline characteristics of the study population are presented in Table 1. Non-participation in the REGASSA trial was similar across treatment groups; 56 participants were lost to follow-up in the TAU group (18%), 49 (15%) in the PE group, and 42 (13%) in the ICBT group. According to the original trial, there was no significant difference between participants and non-participants in age, gender and baseline depression severity. However, those lost to follow-up were more likely to have less somatic comorbidities ($p = 0.01$) and to report more negative RLE ($p < 0.01$). Participation was not associated with exposure to CA ($p = 0.17$). A follow-up survey showed that not participations was mainly related to dissatisfaction with the random allocation of treatment (Hallgren et al., 2016).

Exposure to at least one type of CA was reported by 347 participants (47.08%). The most commonly reported CA was severe emotional difficulties in family (28.62%), followed by parental separation (27.54%), serious long-term financial difficulties (10.45%) and parental loss (4.61%). Participants who reported the occurrence of any CA were, on

Table 1
Baseline characteristics of the study sample by treatment groups: physical exercise (PE), internet based cognitive behavioral therapy (ICBT) and treatment as usual (TAU).

	Total	PE	ICBT	TAU	p-value
	n = 737	n = 249	n = 259	n = 229	
Serious long-term financial difficulties in the family	77 (10.45%)	29 (11.65%)	22 (8.49%)	26 (11.35%)	0.44
Severe emotional difficulties in the family	211 (28.79%)	68 (27.53%)	63 (24.42%)	80 (35.09%)	0.030
Parental separation	203 (27.54%)	60 (24.10%)	67 (25.87%)	76 (33.19%)	0.064
Parental loss	34 (4.61%)	12 (4.82%)	11 (4.25%)	11 (4.80%)	0.94
Total number of childhood adversities	0.71 (0.89)	0.68 (0.86)	0.63 (0.86)	0.84 (0.93)	0.025
Negative recent life events					
None	125 (16.96%)	44 (17.67%)	43 (16.60%)	38 (16.59%)	0.98
One	147 (19.95%)	45 (18.07%)	58 (22.39%)	44 (19.21%)	
Two	163 (22.12%)	57 (22.89%)	56 (21.62%)	50 (21.83%)	
Three	123 (16.69%)	42 (16.87%)	42 (16.22%)	39 (17.03%)	
Four	81 (10.99%)	28 (11.24%)	24 (9.27%)	29 (12.66%)	
Five or more	98 (13.30%)	33 (13.25%)	36 (13.90%)	29 (12.66%)	
Total number of negative recent life events	2.25 (1.62)	2.26 (1.63)	2.21 (1.62)	2.28 (1.61)	0.88
Age	43.28 (12.27)	42.62 (12.37)	43.76 (12.33)	43.45 (12.10)	0.56
Sex					
male	205 (27.82%)	80 (32.13%)	74 (28.57%)	51 (22.27%)	0.053
female	532 (72.18%)	169 (67.87%)	185 (71.43%)	178 (77.73%)	
Baseline depression severity (MADRS score)	21.60 (7.03)	22.20 (6.86)	21.59 (6.75)	20.96 (7.47)	0.16
Follow up depression severity (MADRS score)	12.12 (8.11)	11.38 (7.86)	11.20 (7.35)	13.98 (8.90)	< 0.001
Family history of mental health disorders	371 (51.03%)	114 (46.53%)	136 (53.33%)	121 (53.30%)	0.22
Tertiary education	306 (41.52%)	102 (40.96%)	116 (44.79%)	88 (38.43%)	0.35
Past depressive episodes	429 (59.50%)	146 (59.84%)	152 (60.56%)	131 (57.96%)	0.84
Number of comorbidities	1.27 (1.49)	1.22 (1.29)	1.31 (1.67)	1.29 (1.50)	0.77
Use of antidepressants	213 (28.90%)	76 (30.52%)	81 (31.27%)	56 (24.45%)	0.20

Data are presented as mean (SD) for continuous measures, and n (%) for categorical measures. ANOVA was used to compare continuous outcomes and Chi^2 for the comparison of categorical variables across treatment groups.

average, younger (42.05 years, SD 12.21 vs. 44.35 years, SD 12.25, p = 0.01), had a higher baseline severity of depressive symptoms (22.33, SD 7.06 vs 21.06, SD 6.99, p = 0.02), a higher frequency of familial mental health issues (58.75% vs 44.12%, p < 0.01) and past depressive episodes (65.88% vs. 53.74%, p < 0.01). Importantly, report of CA was associated with report of three or more RLE (45.10% vs 36.90%, p = 0.03).

The mean number of negative RLE reported was 2.25 (SD:1.62), and a total of 290 (40.79%) participants reported experiencing three or more negative RLE in the year prior to enrolment in the study. Those exposed were more likely to report family history of adverse mental health (58.28% vs 46.08%, p < 0.01), and somatic comorbidities (66.55% vs 54.63%, p < 0.01).

3.2. Associations between CA, RLE and treatment outcomes

After adjusting for confounders, exposure to CA was marginally associated with higher baseline depression severity (β = 0.51, 95% CI: −0.01 to 1.02, p = 0.055) Fig. 1.

At follow-up, exposure to a higher number of CA was significantly associated with depression severity (β = 0.79, 95% CI: 0.14 to 1.44, p = 0.02). Response to treatment was also reduced, although this difference was not statistically significant (RR = 0.94, 95% CI: 0.86 to 1.03, p = 0.20). The number of reported negative RLE was significantly associated with both a higher severity of depression (β = 0.52, 95% CI: 0.17 to 0.88, p < 0.01), and lower rates of response to treatment after three months (RR = 0.95, 95% CI: 0.90 to 0.99, p = 0.03) (Fig. 2).

The interaction between exposure to CA and RLE had no effect on depression severity (β = 0.10, 95% CI: −2.12 to0.41, p < 0.53) or in the rates of response to treatment (RERI = −0.04, 95%CI: −0.32 to 0.23, p = 0.78 and AP = −0.05, 95%CI -0.42 to 0.32, p = 0.78) after three months (Table 2).

4. Discussion

This study found that among people with mild to moderate depression treated in primary care with non-pharmacological interventions, those exposed to childhood adversities (CA) or negative recent life events (RLE) had a higher post treatment depression severity and lower rates of treatment response, although with modest effect sizes. Also, there was no significant additive interaction between the effects of CA and those of RLE in the outcomes of non-pharmacological treatments in primary care.

4.1. Strengths and limitations

The strengths of this study include the prospective study design (adapted from the original RCT) with a high response rate (78%). Another strength is the focus on the primary care setting and non-pharmacological interventions for depressive disorders, as these interventions have become recommended for the early treatment for mild to moderate depression, alone or in combination with antidepressants.

Some limitations of this study should also be taken into consideration. This study is a secondary analysis of a randomized controlled trial and both expossures (CA and negative RLE) were assessed retrospectively and using non-standardized self-reported questionnaires at baseline among participants who were already presenting symptoms of depression. This raises the possibility of misclassification of exposure. In the cross-sectional analysis, differential misclassification of the exposure introduced because of recall bias may have led to bias estimates of associations between CA and RLE and the baseline severity of depression. However, for the prospective analysis of treatment outcomes, non-differential misclassification of does not affecting the validity of the observed associations.

Two important CA mentioned in literature, i.e. abuse and neglect during childhood, were not addressed. Even though they have been commonly measured in population-based studies, ethical concerns of clinical trials are different. Previous research shows that childhood adversities tend to occur in clusters, and the cumulative effect almost certainly poses a greater risk of depression in later life than individual events (Gelder, 2000).

For the measurement of negative RLE, a checklist questionnaire was

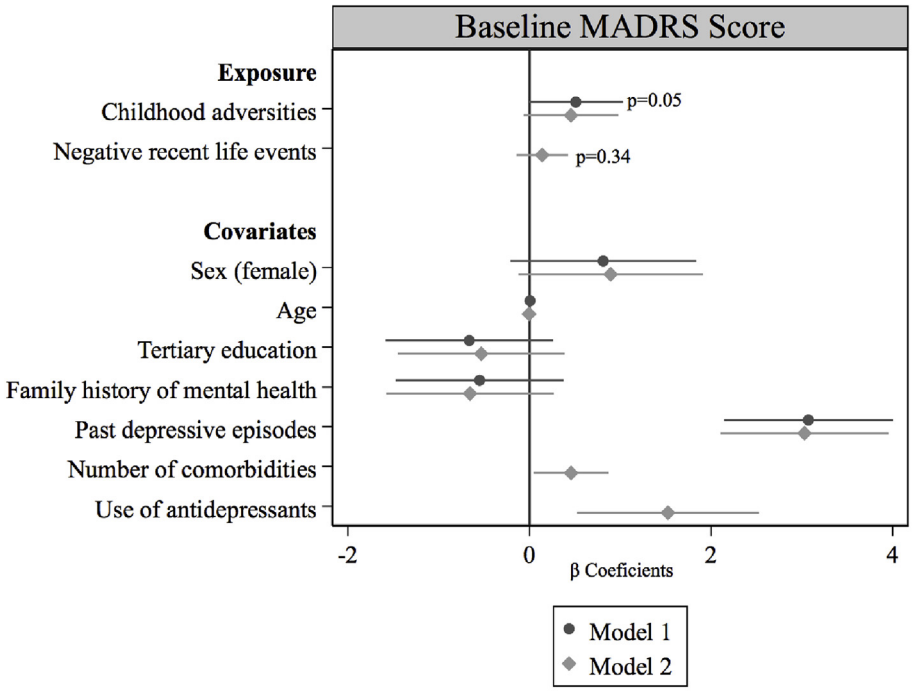

Fig. 1. Estimates and 95% confidence intervals of the linear regression for the association between childhood adversities and negative recent life events with the baseline severity of depression (MADRS score).
Model 1: Childhood adversities as main exposure and sex, age, level of education, family history of mental health disorders and past depressive episodes as covariates. The linear model showed F(6, 885) = 8.75, $p < 0.01$ and $R^2 = 5\%$.
Model 2: Negative recent life events as main exposure and sex, age, level of education, family history of mental health disorders, past depressive episodes, number of comorbidities and use of antidepressants as covariates. The model showed F (9,882) = 7.66,$p < 0.01$ and $R^2 = 7\%$.

used, Several issues arise with the use of self-reported checklists, as they tend to be less reliable and to underestimate the number of significant events compared to more complex semi-structured methods (Brown et al., 2010). However, the use of more sophisticated methods is also more time and resource consuming and was not feasible during the conduction of the REGASSA trial. Finally, the inter-rater reliability between treatment providers was not assessed for this study. This is because each group in this trial had a different unit of treatment. In the TAU group, treatment was provided by their primary care physician, ICBT was provided online by a centralized provider and the PE intervention was provided by physical trainers in the local sport facility of the participating facilities in six different municipalities. However, all treatment providers received training by the study staff regarding the study protocol previous to the trial conduction. Furthermore, the pragmatic design permits evaluation of the effectiveness of these interventions in a real-world setting.

4.2. Implications for future research and public health

The current study adds the observation that both CAs and in particular RLEs are associated with worse treatment outcomes. Identifying predictors of response to treatment of depression is important for both clinical practice and public health policies, as this can help clinicians to stratify patients according to their risk of non-response or response to

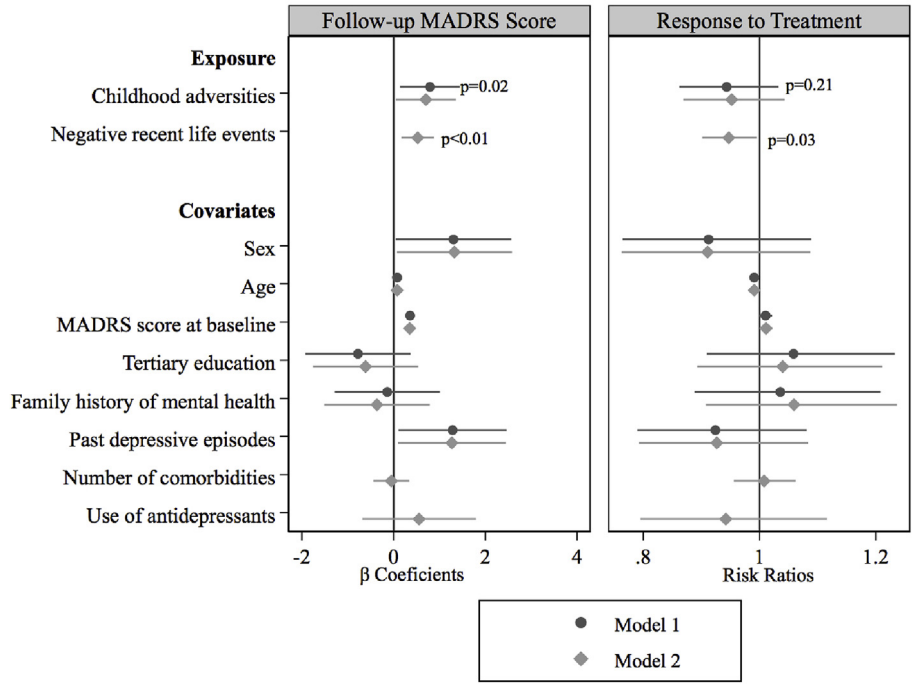

Fig. 2. Estimates and 95% confidence intervals of the linear and Poisson regression models showing the effect of childhood adversities and negative recent life events on follow-up MADRS score and rates of response to treatment.
Model 1: Childhood adversities as main exposure and sex, age, baseline MADRS score, level of education, family history of mental health disorders and past depressive episodes as covariates. The linear regression showed F (7, 699) = 17.17, $p < 0.01$ and $R^2 = 15\%$. In the Poisson regression model, the Akaike information criteria (AIC) was 1.69.
Model 2: Negative recent life events as main exposure and sex, age, baseline MADRS score, level of education, family history of mental health disorders, past depressive episodes, number of comorbidities and the use of antidepressants as covariates. The linear regression showed F (10,696) = 12.77, $p < 0.01$ and $R^2 = 14\%$. The Poisson regression AIC was 1.69.

Table 2
Interaction between childhood adversities and recent life events on treatment outcomes.

	Estimate (95% Confidence Interval)	p value
Depression Severity[a]		
Childhood adversities (CA)	0.41 (−0.65 to 1.48)	0.45
Negative recent life events (RLE)	0.33 (−0.06 to 0.72)	0.63
Interaction term (CA*RLE)	0.10 (−2.12 to 0.41)	0.53
Response to treatment[b]		
RERI	−0.04 (−0.32 to 0.23)	0.78
AP	−0.05 (−0.42 to 0.32)	0.78

RERI: Relative excess due to interaction, AP: Attributable proportion due to interaction. Interaction is present if RERI or AP ≠ 0.

[a] Beta coefficients of the linear regression model including the interaction term (CA*RLE) as a covariate.

[b] Epidemiological measures of interaction (RERI and AP). Dichotomized measures of exposures to CA and RLE were used.

different treatment options during early stages of the diagnostic process. It may also help in the development of targeted interventions based on the population's known characteristics and optimize patient outcomes (Papakostas and Fava, 2008).

Clinicians involved in the treatment of mood disorders in primary care settings should be mindful of the impact of environmental stress, such as negative recent life events or history of childhood adversities, and consider screening for these issues during the course of treatment when appropriate.

Further research is needed to identify moderators and mediators of outcomes for different treatment options (and their combinations) in order to improve the mechanisms of these and other associations and to inform selection of treatment options for depression in primary care (Kraemer et al., 2002).

Authors contributions

All listed authors made significant contributions to the present study. DY, MH and YF conceptualized and design the study, DY performed the statistical analysis and drafted the manuscript, MH and YF made significant contributions to the intellectual content of the manuscript.

Declarations of interest

None.

Disclosure of funding and conflicts of interest

The REGASSA project was funded by Stockholm, Skåne, Kronoberg, Västra Götaland, Blekinge and Västmanland county councils, and REHSAM through the Vårdal Foundation. The funding sources had no role in study design, data collection, data analysis, data interpretation or writing of this manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

The authors would like to thank the research and clinical staff involved in the REGASSA trial. We also thank Dr. Andreas Lundin for his valuable comments during the development of this study, and Filip Andersson for his advice regarding the statistical analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.01.004.

References

Andersson, T., Alfredsson, L., Kallberg, H., Zdravkovic, S., Ahlbom, A., 2005. Calculating measures of biological interaction. Eur. J. Epidemiol. 20 (7), 575–579.
Bellis, M.A., Lowey, H., Leckenby, N., Hughes, K., Harrison, D., 2014. Adverse childhood experiences: retrospective study to determine their impact on adult health behaviours and health outcomes in a UK population. J. Public Health 36 (1), 81–91.
Bock, C., Bukh, J.D., Vinberg, M., Gether, U., Kessing, L.V., 2009. Do stressful life events predict medical treatment outcome in first episode of depression? Soc. Psychiatr. Psychiatr. Epidemiol. 44 (9), 752.
Brown, G.W., Harris, T.O., Kendrick, T., Chatwin, J., Craig, T.K., Kelly, V., Mander, H., Ring, A., Wallace, V., Uher, R., 2010. Antidepressants, social adversity and outcome of depression in general practice. J. Affect. Disord. 121 (3), 239–246.
Carter, G.C., Cantrell, R.A., Victoria, Z., Haynes, V.S., Phillips, G., Alatorre, C.I., Goetz, I., Paczkowski, R., Marangell, L.B., 2012. Comprehensive review of factors implicated in the heterogeneity of response in depression. Depress. Anxiety 29 (4), 340–354.
Davidson, S.K., Harris, M.G., Dowrick, C.F., Wachtler, C.A., Pirkis, J., Gunn, J.M., 2015. Mental health interventions and future major depression among primary care patients with subthreshold depression. J. Affect. Disord. 177, 65–73.
Dohrenwend Bruce, P., Link Bruce, G., Kern, R., Shrout Patrick, E., Markowitz, J., 2006. Measuring life events: the problem of variability within event categories. Stress Med. 6 (3), 179–187.
Donker, T., Batterham, P.J., Warmerdam, L., Bennett, K., Bennett, A., Cuijpers, P., Griffiths, K.M., Christensen, H., 2013. Predictors and moderators of response to internet-delivered interpersonal psychotherapy and cognitive behavior therapy for depression. J. Affect. Disord. 151 (1), 343–351.
Falola, M.I., Limdi, N., Shelton, R.C., 2017. Clinical and genetic predictors of delayed remission after multiple levels of antidepressant treatment: toward early identification of depressed individuals for advanced care options. J. Clin. Psychiatr. 78 (9), e1291–e1298.
Forsell, Y., 2007. A three-year follow-up of major depression, dysthymia, minor depression and subsyndromal depression: results from a population-based study. Depress. Anxiety 24 (1), 62–65.
G.B.D. DALYs, HALE Collaborators, 2017. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390 (10100), 1260–1344.
Gaynes, B.N., Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Balasubramani, G.K., McGrath, P.J., Thase, M.E., Klinkman, M., Nierenberg, A.A., Yates, W.R., Fava, M., 2008. Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. J. Gen. Intern. Med. 23 (5), 551–560.
Gelder, M.G., 2000. New Oxford Textbook of Psychiatry. Oxford. Oxford Univ Press, Oxford.
Hallgren, M., Helgadottir, B., Herring, M.P., Zeebari, Z., Lindefors, N., Kaldo, V., Ojehagen, A., Forsell, Y., 2016. Exercise and internet-based cognitive-behavioural therapy for depression: multicentre randomised controlled trial with 12-month follow-up. Br. J. Psychiatry 209 (5), 414–420.
Hallgren, M., Kraepelien, M., Ojehagen, A., Lindefors, N., Zeebari, Z., Kaldo, V., Forsell, Y., 2015. Physical exercise and internet-based cognitive-behavioural therapy in the treatment of depression: randomised controlled trial. Br. J. Psychiatry 207 (3), 227–234.
Helgadottir, B., Forsell, Y., Hallgren, M., Moller, J., Ekblom, O., 2017. Long-term effects of exercise at different intensity levels on depression: a randomized controlled trial. Prev. Med. 105, 37–46.
Holmes, T.H., Rahe, R.H., 1967. The social readjustment rating scale. J. Psychosom. Res. 11 (2), 213–218.
Horesh, N., Klomek, A.B., Apter, A., 2008. Stressful life events and major depressive disorders. Psychiatr. Res. 160 (2), 192–199.
Jain, F.A., Hunter, A.M., Brooks 3rd, J.O., Leuchter, A.F., 2013. Predictive socioeconomic and clinical profiles of antidepressant response and remission. Depress. Anxiety 30 (7), 624–630.
Keers, R., Uher, R., Gupta, B., Rietschel, M., Schulze, T.G., Hauser, J., Skibinska, M., Henigsberg, N., Kalember, P., Maier, W., Zobel, A., Mors, O., Kristensen, A.S., Kozel, D., Giovannini, C., Mendlewicz, J., Kumar, S., McGuffin, P., Farmer, A.E., Aitchison, K.J., 2010. Stressful life events, cognitive symptoms of depression and response to antidepressants in GENDEP. J. Affect. Disord. 127 (1–3), 337–342.
Kendler, K.S., Karkowski, L.M., Prescott, C.A., 1998. Stressful life events and major depression: risk period, long-term contextual threat, and diagnostic specificity. J. Nerv. Ment. Dis. 186 (11), 661–669.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama 289 (23), 3095–3105.
Kessler, R.C., Davis, C.G., Kendler, K.S., 1997. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. Psychol. Med. 27 (5), 1101–1119.
Kessler, R.C., McLaughlin, K.A., Green, J.G., Gruber, M.J., Sampson, N.A., Zaslavsky, A.M., Aguilar-Gaxiola, S., Alhamzawi, A.O., Alonso, J., Angermeyer, M., Benjet, C., Bromet, E., Chatterji, S., de Girolamo, G., Demyttenaere, K., Fayyad, J., Florescu, S., Gal, G., Gureje, O., Haro, J.M., Hu, C.Y., Karam, E.G., Kawakami, N., Lee, S., Lepine, J.P., Ormel, J., Posada-Villa, J., Sagar, R., Tsang, A., Ustun, T.B., Vassilev, S., Viana, M.C., Williams, D.R., 2010. Childhood adversities and adult psychopathology in the WHO world mental health surveys. Br. J. Psychiatry 197 (5), 378–385.
Klein Daniel, N., Arnow Bruce, A., Barkin Jennifer, L., Dowling, F., Kocsis James, H., Leon Andrew, C., Manber, R., Rothbaum Barbara, O., Trivedi Madhukar, H., Wisniewski Stephen, R., 2009. Early adversity in chronic depression: clinical correlates and

response to pharmacotherapy. Depress. Anxiety 26 (8), 701–710.
Korkeila, J., Vahtera, J., Nabi, H., Kivimaki, M., Korkeila, K., Sumanen, M., Koskenvuo, K., Koskenvuo, M., 2010. Childhood adversities, adulthood life events and depression. J. Affect. Disord. 127 (1–3), 130–138.
Kraemer, H.C., Wilson, G.T., Fairburn, C.G., Agras, W.S., 2002. Mediators and moderators of treatment effects in randomized clinical trials. Arch. Gen. Psychiatr. 59 (10), 877–883.
Linde, K., Kriston, L., Rucker, G., Jamil, S., Schumann, I., Meissner, K., Sigterman, K., Schneider, A., 2015a. Efficacy and acceptability of pharmacological treatments for depressive disorders in primary care: systematic review and network meta-analysis. Ann. Fam. Med. 13 (1), 69–79.
Linde, K., Sigterman, K., Kriston, L., Rucker, G., Jamil, S., Meissner, K., Schneider, A., 2015b. Effectiveness of psychological treatments for depressive disorders in primary care: systematic review and meta-analysis. Ann. Fam. Med. 13 (1), 56–68.
Lundin, A., Forsell, Y., Dalman, C., 2017. Mental health service use, depression, panic disorder and life events among Swedish young adults in 2000 and 2010: a repeated cross-sectional population study in Stockholm County, Sweden. Epidemiol. Psychiatr. Sci. 1–9.
Manea, L., Gilbody, S., McMillan, D., 2012. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. CMAJ (Can. Med. Assoc. J.) 184 (3), E191–E196.
Mazure, C.M., Bruce, M.L., Maciejewski, P.K., Jacobs, S.C., 2000. Adverse life events and cognitive-personality characteristics in the prediction of major depression and antidepressant response. Am. J. Psychiatry 157 (6), 896–903.
McLaughlin, K.A., Conron, K.J., Koenen, K.C., Gilman, S.E., 2010. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. Psychol. Med. 40 (10), 1647–1658.
Melas, P.A., Guban, P., Rahman, M.S., Lavebratt, C., Forsell, Y., 2018. Neuropeptide Y, stressful life events and personality trait conscientiousness: preliminary associations from a Swedish longitudinal study. Psychiatr. Res. 263, 48–53.
Möller, J., Theorell, T., de Faire, U., Ahlbom, A., Hallqvist, J., 2005. Work related stressful life events and the risk of myocardial infarction. Case-control and case-crossover analyses within the Stockholm heart epidemiology programme (SHEEP). J. Epidemiol. Community Health 59 (1), 23.
National Institute for Health and Care Excellence, 2009. In: NICE (Ed.), Depression in Adults: Recognition and Management. NICE, London.
Papakostas, G.I., Fava, M., 2008. Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder. Dialogues Clin. Neurosci. 10 (4), 439–451.
Rahe, R.H., Floistad, I., Bergan, T., Ringdal, R., Gerhardt, R., Gunderson, E.K., Arthur, R.J., 1974. A model for life changes and illness research. Cross-cultural data from the Norwegian Navy. Arch. Gen. Psychiatr. 31 (2), 172–177.
Riedel, M., Möller, H.-J., Obermeier, M., Schennach-Wolff, R., Bauer, M., Adli, M., Kronmüller, K., Nickel, T., Brieger, P., Laux, G., Bender, W., Heuser, I., Zeiler, J., Gaebel, W., Seemüller, F., 2010. Response and remission criteria in major depression – a validation of current practice. J. Psychiatr. Res. 44 (15), 1063–1068.
Schuch, F.B., Dunn, A.L., Kanitz, A.C., Delevatti, R.S., Fleck, M.P., 2016. Moderators of response in exercise treatment for depression: a systematic review. J. Affect. Disord. 195, 40–49.
Singla, D.R., Kohrt, B.A., Murray, L.K., Anand, A., Chorpita, B.F., Patel, V., 2017. Psychological treatments for the world: lessons from low- and middle-income countries. Annu. Rev. Clin. Psychol. 13, 149–181.
Socialstyrelsen, 2016. Nationella riktlinjer för vård vid depression och ångestsyndrom. Stöd för styrning och ledning. In: Socialstyrelsen (Ed.), Socialstyrelsen (The National Board of Health and Welfare), Stockholm.
Statacorp, 2017. Stata Statistical Software: Release 15. StataCorp LLC, College Station, TX.
Stubbs, B., Vancampfort, D., Hallgren, M., Firth, J., Veronese, N., Solmi, M., Brand, S., Cordes, J., Malchow, B., Gerber, M., Schmitt, A., Correll, C.U., De Hert, M., Gaughran, F., Schneider, F., Kinnafick, F., Falkai, P., Moller, H.J., Kahl, K.G., 2018. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and position statement from the european psychiatric association (EPA), supported by the international organization of physical therapists in mental health (IOPTMH). Eur. Psychiatry 54, 124–144.
Theorell, T., 2012. Evaluating life events and chronic stressors in relation to health: stressors and health in clinical work. Adv. Psychosom. Med. 32, 58–71.
Tiet, Q.Q., Bird, H.R., Hoven, C.W., Moore, R., Wu, P., Wicks, J., Jensen, P.S., Goodman, S., Cohen, P., 2001. Relationship between specific adverse life events and psychiatric disorders. J. Abnorm. Child Psychol. 29 (2), 153–164.
Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., Team, S.D.S., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am. J. Psychiatry 163 (1), 28–40.
Tunvirachaisakul, C., Gould, R.L., Coulson, M.C., Ward, E.V., Reynolds, G., Gathercole, R.L., Grocott, H., Supasitthumrong, T., Tunvirachaisakul, A., Kimona, K., Howard, R.J., 2018. Predictors of treatment outcome in depression in later life: a systematic review and meta-analysis. J. Affect. Disord. 227, 164–182.
Tylee, A., Gandhi, P., 2005. The importance of somatic symptoms in depression in primary care. Prim. Care Companion J. Clin. Psychiatry 7 (4), 167–176.
You, S., Conner, K.R., 2009. Stressful life events and depressive symptoms: influences of gender, event severity, and depression history. J. Nerv. Ment. Dis. 197 (11), 829–833.
Zimmerman, N., 2018. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. Med. J. Aust. 209 (1), 43.
Zou, G., 2004. A modified Poisson regression approach to prospective studies with binary data. Am. J. Epidemiol. 159 (7), 702–706.