Journal of Affective Disorders 299 (2022) 559–567

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Association of childhood maltreatment and cortisol with the severity and stability of depression symptoms

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ARTICLE INFO

Keywords:
Depression symptoms
Cortisol
Childhood maltreatment
Age
Latent class analysis

ABSTRACT

Background: Little is known about patterns of depression symptoms over time in older adults. This study aims to assess the association of childhood maltreatment and cortisol levels with latent classes of depression symptoms over ten years in older adults.

Methods: A total of 752 participants (mean age 61.7±9.5, female 18%) in the Second Manifestations of ARTerial disease-Memory, depression and aging (SMART-Medea) study provided up to twenty measures of depression symptoms over ten years based on the Patient Health Questionnaire-9 (PHQ-9). At baseline, salivary cortisol was measured, and childhood maltreatment was assessed. Responses to the PHQ-9 were indicators in a latent class analysis. Multinomial regression determined associations between class membership and cortisol and maltreatment, adjusting for age, sex, and education.

Results: Four distinct classes were identified; never depressed (n=275, 37%), energy/sleep difficulties (n=237, 32%), mild depression symptoms (n=152, 20%) and fluctuating severe depression (n=88, 12%). Childhood maltreatment was associated with mild depression symptoms (OR=1.95, 95% CI: 1.17-3.25) and fluctuating severe depression (OR=3.50, 95% CI: 1.99-6.15). Blunted morning cortisol was associated with energy/sleep difficulties (OR=0.98, 95% CI: 0.95-1.00) and fluctuating severe depression (OR=0.96, 95% CI: 0.92-0.99). There was no evidence for interaction between maltreatment and cortisol.

Limitations: There is limited generalizability due to the cohort consisting of participants with atherosclerosis and being mostly male. This study utilizes retrospective self-reporting of childhood maltreatment.

Conclusion: Childhood maltreatment and blunted morning cortisol independently contribute to a worse depression course. Blunted morning cortisol may contribute to sub-clinical depression symptoms, specifically difficulties with energy levels and sleep.

1. Introduction

Major Depression Disorder (MDD) is a highly prevalent mental disorder with significant consequences, on both the individual and societal level; depression has been associated with decreased functioning, loss of work productivity, and physical health consequences, including cardiovascular disease and obesity (Beurel et al., 2020; Brown et al., 2009; Hare et al., 2014; McIntyre et al., 2006; Penninx, 2017; Simon, 2003; Zhang et al., 2018). The direct costs of depression, including prescription drugs and medical services, were nearly $100 billion in 2010 in the United States (Greenberg et al., 2015). MDD is most prevalent in young and middle-aged adults, while in older age groups the 12-month prevalence of MDD decreases (Hasin et al., 2018). However, adults in later life may actually experience more symptoms of depression compared to younger populations (Licht-Strunk et al., 2005; Wang et al., 2017).

Studies assessing depression in a longitudinal manner have shown that the course of symptoms is often more chronic in older populations, compared to younger adults (Bruin et al., 2018; Licht-Strunk et al., 2007). Furthermore, assessing these symptoms over an extended period of time is critical; a single assessment of depression at a given time point

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[1] Listed in acknowledgments

https://doi.org/10.1016/j.jad.2021.12.036
Received 29 October 2020; Received in revised form 9 December 2021; Accepted 17 December 2021
Available online 20 December 2021

may be misleading, as this only provides information about depression status at that time, without accounting for chronicity or fluctuations of the condition (Verduijn et al., 2017). It is also possible for individuals with depression symptoms, but no clinical diagnosis, to experience diminished physical health and quality of life (Chachamovich et al., 2008; Rucci, 2003; Schweizer et al., 2018), making it critical to investigate the etiology of such symptoms.

Understanding the risk factors for worse depression symptoms over time in older adults may provide important insights for treatment and prevention of symptoms over time. An established risk factor for a worse depression course in adults and older adults is early life trauma, specifically childhood maltreatment (Comijs et al., 2013; Nelson et al., 2017) which may consist of physical, sexual, or psychological abuse, as well as emotional neglect. Alterations to stress-response systems, specifically the hypothalamus-pituitary-adrenal (HPA) axis, as a result of prolonged stress in early development, have been proposed as a connection between childhood maltreatment and subsequent depression symptoms (Mayer et al., 2020; Tarullo and Gunnar, 2006). The HPA-axis is an important neuroendocrine pathway responsible for regulating levels of the stress hormone cortisol, which can be measured to indicate the health of this system. However, the relationship between early-life stress and HPA-axis dysregulation, as measured by cortisol levels, is not entirely understood. A recent review and meta-analysis found a great deal of heterogeneity in cortisol levels in adults with a history of early life stress, as some studies find these subjects have higher basal cortisol, while others find that cortisol is blunted; the authors subsequently concluded that there was no significant relationship between early life stress and cortisol (Fogelman and Canli, 2018). Similarly, the relationship between cortisol and depression symptoms is somewhat heterogeneous, as depression has been associated with both blunted and heightened cortisol awakening response (Dedovic and Ngiam, 2015). Clearly, more research is needed to determine to what extent childhood maltreatment may disrupt the HPA-axis and contributes to depressive symptoms. While several studies have reported independent and interaction effects of early life stress and cortisol levels on depression symptoms (Schuler et al., 2017; Shapero et al., 2019), very few studies of this nature have been conducted in an older population. Furthermore, few studies have an extended follow-up period that allows for long-term assessment of the severity and stability of depression symptoms over time. Consequently, the enduring effects of childhood maltreatment and HPA-axis functioning on long-term patterns of depression symptoms later in life are poorly understood.

1.1. Aims of the study

This study aimed to 1) establish latent classes based on repeated measures of depression symptoms during 10 years of follow-up, and 2) assess childhood maltreatment, HPA-axis functionality, and their interaction, as predictors of latent class membership in a cohort of older adults with atherosclerosis, due to the increased prevalence of depression in people with cardiovascular disease. We predict that participants reporting childhood maltreatment will have more severe depression symptoms and that individuals with more severe depression will demonstrate dysregulated HPA-axis functioning.

2. Methods

2.1. Participants

This study utilized data from the SMART-Medea study, a prospective cohort study among individuals with a history of arterial disease, given the increased prevalence of depression in this population. SMART-Medea is an ancillary study to the Second Manifestations of ARTerial disease—Magnetic Resonance (SMART-MR) study (described in further detail elsewhere (Geerlings et al., 2009)). Between May 2001 and December 2005, 1309 newly referred patients to University Medical Center Utrecht were enrolled in the SMART-MR study with any of the following; coronary artery disease, cerebrovascular disease, peripheral arterial disease, or abdominal aortic aneurysm. Between January 2006 and May 2009, surviving participants were invited to participate in the SMART-Medea study, resulting in 752 participants (n=71 died; n=466 refused or did not respond; n=18 were lost to follow-up; n=2 did not complete any depression questionnaires). Data was collected in a 1-day visit to University Medical Center (UMC) Utrecht and included a physical examination, blood and urine sampling, and neuropsychological and depression assessments.

Questionnaires that were answered at home before the visit to the UMC Utrecht assessed demographics, including age, sex, and education, as well as risk factors and medical history, depression symptoms, and medication use. Also, saliva sampling for cortisol levels was done at home. Beginning in July 2008, depression symptom questionnaires were sent to participants biannually. Data collection and examinations of all 752 participants took place until May 2009, leading to overlap in the timeline of measurements (Kooistra et al., 2016). In addition, not all participants completed the depression symptoms questionnaire every six months. Consequently, participants have varying durations of follow-up and numbers of completed questionnaires (see Table S1 for number of questionnaires per follow-up point).

2.2. Depression symptoms

Depression symptoms were measured with the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001; Zuithoff et al., 2010). The PHQ-9 assesses the presence of nine DSM-IV criteria in the previous two weeks on a 4-point scale, ranging from 0 (“not at all”) to 3 (“nearly every day”), with a total sum score range of 0–27, with higher scores indicating increasing symptom severity. Total PHQ-9 score at each time point was treated as a continuous variable, and the mean and variance for each individual were used to derive latent classes.

2.3. Assessment of childhood maltreatment

Childhood maltreatment was assessed using The Netherlands Mental Health Survey and Incidence Study (NEMESIS) Trauma Interview (Spijker et al., 2002). Participants were asked whether they experienced any of the following before age 16: emotional neglect, psychological abuse, physical abuse, and/or sexual trauma. Emotional neglect was defined as ‘people at home didn’t listen to you, your problems were ignored, and you felt unable to find (receive/obtain) any attention or support from the people in your house.’ Psychological abuse was defined as ‘you were cursed at, unjustly punished, your brothers and sisters were favored – but no bodily harm was done.’ Physical abuse was defined as ‘you were abused physically, meaning being hit, kicked, beaten up or other types of physical abuse’ and sexual abuse was defined as ‘you were sexually abused, meaning being touched or having to touch someone in a sexual way against your will.’

The number of maltreatment types experienced was combined with the frequency of maltreatment, resulting in a sum square ranging from 0 to 8 (Peyrot et al., 2014). In the analysis, participants were dichotomized as having ever experienced any of the four types of maltreatment. In subsequent analyses, subjects were dichotomized as ever having ever experienced each of the four types of maltreatment to compare potential differences.

2.4. HPA axis activity

HPA axis activity was assessed at home with seven measurements of salivary cortisol over a 24-hour period. Saliva was collected using dental cotton rolls (Salivette, Sarstedt, Nümbrecht, Germany). The first sample was collected at awakening, and samples were collected 30, 45, and 60 min thereafter, and at 10 pm and 11 pm. After the final sample, participants were instructed to take a low dose of dexamethasone (0.5 mg),

and sample saliva the next morning at awakening. In addition to the raw cortisol measures, two measures of morning cortisol were calculated using formulas by Pruessner et al. (Pruessner et al., 2003): 1) the area under the curve with respect to the increase (AUCi), which measures the dynamic of the cortisol awakening response (CAR) and is more related to the sensitivity of the system, emphasizing changes over time and 2) the area under the curve with respect to ground (AUCg), which measures the total cortisol secretion in the first hour after awakening. Evening cortisol was calculated as the mean of measurements taken at 10 PM and 11PM.

2.5. Covariates

Education level was measured using eight categories, ranging from primary school to academic degree. Presence of cardiovascular disease was binary for each of the possible diseases, i.e., coronary artery disease, ischemic stroke, peripheral arterial disease, or abdominal aortic aneurysm. Smoking status was divided into current, former, or never smokers. Diabetes mellitus was indicated by one or more of the following: history of diabetes mellitus, glucose $\geq$7.0 mmol/L, or self-reported use of oral antidiabetic drugs or insulin. Alcohol consumption was measured in drinks consumed per day.

2.6. Statistical analysis

Baseline participant characteristics were calculated for the total study sample and for classes of individuals, and compared with general linear models and chi-square analyses. Data analysis and modeling were performed using MPlus Version 6.12 (Muthén and Muthén, 1998-2010) and R software (R Core Team, 2018), including packages for graphics (Wickham, 2016), descriptive analysis (Yoshida, 2019), multinomial logistic regression (Venables and Ripley, 2002), and multiple helper functions (Dowle and Srinivasan, 2019; Robinson and Hayes, 2019; Wickham, 2011; Wickham et al., 2019; Wickham and Henry, 2019; Wickham and Miller, 2019).

Latent class analysis (LCA) was performed using Mplus in order to identify groups of individuals based on similar patterns of PHQ-9 responses. LCA assumes that an unobserved, categorical variable accounts for differences or similarities in symptom profiles (Henry and Muthen, 2010). Individuals are assigned to different classes based on their posterior probabilities of being in a given class. The number of latent classes is determined by starting with a 1-class model and adding subsequent classes with the upper limit based on previous literature plus one. LCA is typically used in cross-sectional studies to identify underlying groups based on observed measurements. However, methods typically used for longitudinal data, such as growth mixture modeling or latent class growth analysis, would characterize depression as a function of time (Feldman et al., 2009), while it is more likely that depression symptoms fluctuate in a non-continuous manner over time (Bjerkeset et al., 2008; January et al., 2014). LCA was therefore used in this study to accommodate the high variation in PHQ-9 responses and relatively high frequency of observations (Feldman et al., 2009).

In the LCA, the mean and variance of participants' PHQ-9 scores over time were included as indicator variables in a multilevel model and were allowed to vary between classes. The mean score accounts for the severity of depression, while the variation represents the stability of PHQ-9 score over time. Models for 1-5 classes were computed and compared using Akaike's information criterion (AIC), Bayesian information criterion (BIC), sample-size adjusted BIC, entropy, the bootstrap likelihood ratio test (BLRT), and the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT). AIC, BIC, and SaBIC are used to compare goodness of fit of models, where the smaller value indicates the better fit. Entropy measures the accuracy of latent classification, with higher values representing better classification and a value above 0.8 being considered acceptable. In order to determine the best fitting model, models that included one or two classes with a variance fixed at 1 were computed to test the hypothesis that participants with very high or very low scores may fluctuate less over time. Missing PHQ-9 data was handled using full-information maximum likelihood.

To determine the effect of predictors on latent classification, class membership was exported from Mplus and appended to the complete dataset in R. Missing cortisol data was imputed using multiple imputation R package mice (10 sets) and the results were pooled (van Buuren and Groothuis-Oudshoorn, 2011). Multinomial logistic regression models were used to determine the predictors of class membership. In model 1, the categorical latent class was first regressed on age, sex/-gender, and level of education, with the non-depressed group as the reference category. All subsequent models were adjusted for these variables. Models 2 and 3 separately assessed abuse and cortisol as predictors of latent class membership. Model 4 adjusted for both abuse and cortisol. The interaction of cortisol and abuse was assessed in Model 5 by including the interaction term to model 4, as well as by stratifying based on ever/never having experienced childhood maltreatment. Model 6 was additionally adjusted for cardiovascular measures and lifestyle factors.

3. Results

There was an overall high response rate of 89% (range 83%-93%) to the PHQ-9 across all time points (Table S1). The total sample consisted of 752 participants (18% women, mean$\pm$SD age 61.7$\pm$9.5), described in Table 1. Cardiovascular health and lifestyle characteristics are described in Table S2. A significant portion of the sample reported some type of childhood maltreatment (20.3%), with emotional neglect being the most common type of neglect (13.3%). History of abuse was more prevalent in women (29.1%) than men (18.3%), and women experienced more of each type of maltreatment compared to men (Table S3).

3.1. Latent class analysis

A four-class model was selected based on the fit parameters given in Table 2 and clinical meaningfulness of the subgroups. Based on the sample size adjusted Bayesian Information Criteria (SSABIC), the four-class model was superior to models with 3 or fewer classes. Furthermore, when a fifth class was added, the additional class was not distinct from the existing first and second classes, represented a small proportion of the sample, and did not fit the data significantly better than a four-class model, per the Adjusted Lo-Mendell-Rubin p-value (0.15). A sixth class was tested, but the model was not able to converge properly.

Mean PHQ-9 scores over time per latent class are given in Figure 1. Groups are described based on their mean score and variability over time: the "never depressed" class (37% prevalence) had very low scores and were very stable across all time points. The "energy/sleep difficulties" class (32% prevalence) was also quite stable, but demonstrated slightly higher, though subclinical, PHQ-9 scores. The majority of PHQ-9 points in this group were due to reported sleep and energy problems, as reported in Table 3. The "mild depression symptoms" class (20% prevalence) had increased variation in symptom severity over time compared to the first two classes, scoring at or near the clinical cut-off of 6 for depression based on PHQ-9 responses (Zuithoff et al., 2010). The "severe fluctuating depression" class (12% prevalence) had quite a high variance and a mean score above the clinical cut-off for the PHQ-9 at each time point.

Demographics, cortisol levels, and psychiatric measures of the identified four classes are given in Table 1. Increasing severity and fluctuation of depression symptoms corresponded with more reported childhood maltreatment, younger age, higher scores on the Beck Anxiety Index (BAI), more MDD diagnoses, and female gender. The never depressed group had the highest morning cortisol measurements compared to all other groups (Table 1).

Table 1
Characteristics of the study population by latent class analysis group, and the total study sample.

	Never depressed (N = 275)	Energy/sleep difficulties (N = 237)	Mild depression symptoms (N = 152)	Fluctuating severe depression (N = 88)	p-value	Total sample (N = 752)
Demographics						
Age (mean ± SD)	61.6±9.1	62.0±9.4	62.7±10.1	59.6±9.6	0.147	61.7±9.5
Education, n (%)					0.021	
Less than high school	11 (4.1)	22 (9.4)	20 (13.2)	15 (17)		68 (9.1)
High school	179 (65.1)	146 (61.6)	99 (65.1)	60 (68.2)		484 (64.4)
College/University	81 (29.5)	66 (27.8)	32 (21.1)	13 (14.8)		192 (25.5)
Women, n (%)	37 (13.5)	34 (14.3)	37 (24.3)	27 (30.7)	<0.001	135 (18)
MDD diagnosis	0 (0)	9 (4.2)	13 (9.3)	29 (36.7)	<0.001	51 (7.5)
History of depression	79 (29.6)	94 (41.0)	78 (51.7)	64 (74.4)	<0.001	315 (43)
Beck Anxiety Index (mean ± SD)	2.3 ±3.1	4.5±4.9	8.4 ±5.8	13.4± 8.4	<0.001	5.5±6.3
Childhood maltreatment, n (%)						
Any abuse	39 (14.4)	41 (17.7)	37 (24.7)	33 (37.9)	<0.001	150 (20.3)
Emotional neglect	23 (8.5)	23 (9.8)	26 (17.3)	27 (30.7)	<0.001	99 (13.3)
Psychological abuse	15 (5.5)	20 (8.6)	11 (7.2)	23 (26.4)	<0.001	69 (9.3)
Physical abuse	15 (5.5)	15 (6.4)	12 (7.9)	15 (17.0)	0.033	57 (7.7)
Sexual assault	10 (3.7)	13 (5.6)	9 (5.9)	10 (11.5)	0.167	42 (5.6)
Cortisol (nmol/l) (mean ± SD)						
Awakening	12.9±6.0	12.6±6.1	12.5±6.5	11.2±6.1	0.330	12.5±6.15
30 minutes	20.1±9.1	18.2±8.8	19.2±9.3	16.2±8.4	0.027	18.9±9.02
45 minutes	19.5±8.4	17.8±8.6	18.6±9.0	16.8±9.1	0.080	18.5±8.69
60 minutes	18.9±12.6	16.2±7.7	16.9±8.1	16.4±8.7	0.086	17.4±10
10 PM	4.3±5.1	4.3±3.7	4.6±5.5	4.0±3.0	0.602	4.3±4.57
Dexamethasone	2.2±2.4	2.4±2.4	2.6±3.5	2.3±2.2	0.512	2.3±2.63
AUCi	5.2±6.3	3.8±5.7	4.7±5.8	4.0±5.9	0.214	4.5±5.99
AUCg	18.0±6.9	16.5±6.8	17.1±7.2	15.1±7.0	0.027	17.0±6.96

MDD = Major Depression Disorder, AUCi = area under the curve with respect to increase, AUCg = area under the curve with respect to ground

Table 2
Fit indices for latent class models among participants with at least one PHQ-9 score.

Classes	Loglikelihood	AIC	BIC	SSABIC	Entropy	Adjusted LMR (p)	BLRT p value
1	-23305.33	46698.65	46902.05	46762.33	—-	—-	—-
2	-18675.80	37485.59	37795.32	37582.57	0.94	71639.66 (0.33)	p < .001
3	-17216.45	34656.89	35174.64	34819.00	0.91	2908.94 (0.00)	p < .001
4	-16855.29	34024.57	34750.34	34251.80	0.89	719.91 (0.11)	p < .001
5	-16610.67	33625.34	34559.13	33917.70	0.88	487.55 (0.15)	p < .001

AIC = Akaike's Information Criteria, BIC = Bayes Information Criteria, SSABIC = Sample size adjusted BIC, LMR=Lo-Mendell-Rubin, BLRT =bootstrap likelihood ratio test

3.2. Relationship between cortisol and depression symptoms

To investigate the relationship between depression symptoms over time and cortisol, curves based on median basal cortisol levels were constructed for each latent class (Figure 2). Differences among classes can be seen in the morning salivary cortisol samples. The "never depressed" class had the highest cortisol levels across the first hour since awakening, while the "severe fluctuating depression" class had a more blunted response and overall lower salivary cortisol levels, compared to the less severely depressed groups. The "energy/sleep difficulties" class, had higher morning cortisol than the "severe fluctuating depression" group, but lower than the "never depressed" and "mild depression symptoms" groups. There was negligible variation between groups in the evening cortisol measurements, and dexamethasone response test. Additional figures demonstrating diurnal cortisol curves stratified by abuse/no abuse and type of abuse can be found in the Supplementary Materials (Figures S1-S4).

3.3. Multinomial logistic regression

Multinomial logistic regression analyses adjusting for age, sex, and educational level showed that, with the never depressed group as a reference, lower morning cortisol, as measured by AUCi, predicted class membership in both "energy/sleep difficulties" (OR=0.96, 95% CI: 0.93-1.00) and "severe fluctuating depression" (OR=0.95, 95% CI: 0.91-1.00), but not mild fluctuating depression (OR=0.99, 95% CI: 0.95-1.03) (Table 4). Similarly, lower AUCg and lower levels of cortisol samples taken at 30, 45, and 60 minutes after awakening were predictive of energy/sleep difficulties and fluctuating depression latent class membership, while evening measures and the measurement taken after dexamethasone administration were not associated with class membership. Abuse was associated with mild depression symptoms (OR=1.95, 95% CI: 1.17-3.25) and severe fluctuating depression (OR=3.50, 95% CI: 1.99-6.15), but not with energy/sleep difficulties (OR=1.28, 95% CI: 0.79-2.06). All types of maltreatment were associated with membership in the fluctuating severe depression group, with psychological abuse (OR=5.26, 95% CI: 2.55-10.86) and emotional neglect (OR=4.79, 95% CI: 2.53-9.07) having the strongest associations. There was no evidence for interaction effects (Table S4 and Table S5). When abuse and cortisol were adjusted for each other, there were no significant changes to either variable's association with depression class membership (Table S6 and Table S7). Controlling for cardiovascular and lifestyle measures did not change these associations (Table S8). When stratifying by sex (Table S9, Table S10), results did not indicate that the association between maltreatment and latent class membership is moderated by sex. In both men and women, history of abuse was associated with fluctuating severe depression (male OR=3.61, 95% CI: 1.89-6.91, female OR=4.03, 95% CI: 1.16-13.97). Associations between morning cortisol, AUCg, or AUCi and depression symptoms did not vary greatly between men and women, however the associations between evening cortisol and cortisol after dexamethasone was increased in men, but not in women, regardless of latent class membership.

Figure 1. Plot of mean PHQ-9 scores per time point, shown as loess curves with 95% confidence interval bands, and stratified by latent class membership.

4. Discussion

We identified four classes of depression symptom patterns in a 10-year follow-up cohort of middle aged and older adults with a history of arterial disease using LCA: never depressed, energy/sleep difficulties, mild depression symptoms, and severe fluctuating symptoms. Energy/sleep difficulties and severe depression symptoms were associated with a flatter morning cortisol curve. Consistent with our hypothesis, childhood maltreatment was associated with both mild and severe depression symptoms, with severe symptoms having the strongest association. Psychological abuse had the strongest association with severe depression symptoms, followed by emotional neglect, which was also the most prevalent type of maltreatment. Interaction terms were not significant, suggesting that HPA-axis and childhood maltreatment act independently on patterns of depression symptoms. The strength of association between childhood maltreatment and severe depression appears to be similar between men and women, though when stratifying by sex, the association between history of abuse and mild depression symptoms appears to diminish. This result may be due to the relatively low number of women in the study population but suggests that there is a weaker association between abuse and mild depression in men.

We employed a novel approach by using a longitudinal latent class analysis to assess the association of severity and stability of depression symptoms with childhood maltreatment and HPA-axis functionality over an extended follow-up. Latent class analysis is typically used in cross-sectional research but was a good option for this study due to the fluctuating patterns of a significant portion of participants PHQ-9 responses over time, making it impractical to fit the data with a growth curve model. Additionally, the first aim of this study was to identify classes based on symptom severity and stability, which are well represented by the mean and variance of PHQ-9 scores over follow-up.

The latent class analysis revealed that a large portion of participants experience very few or no depression symptoms, while a smaller portion experience a more fluctuating, severe course. The group experiencing energy and sleep difficulties, while not depressed, may still experience some of the consequences typically associated with depression as a result of these symptoms. Low energy and difficulty sleeping may be typical effects aging, however it is interesting to note that another study assessing depression symptomology using the PHQ-9 found a similar class of participants (31% of the study population) in an older cohort (Holub et al., 2019). In that study, the class reporting these energy/sleep difficulties also reported worse general health compared to a class with low concerns. Our study found a similarly large (32%) group, which would not be identified when using clinical cut-off scores. While these symptoms may not be attributed to depression, they may indicate lower quality of life and higher risk for comorbidities. Further studies are needed to investigate these relationships.

This study builds on previous knowledge that childhood maltreatment is associated with the incidence of depression by finding a similar association with depression symptoms over a long follow up with a high frequency of observations. A meta-analysis showed that adults with a history of maltreatment were 2.7 to 3.7 times more likely to develop depression (Nelson et al., 2017). This finding is further supported by studies in older adults that have found an association between childhood

Table 3
Response to PHQ-9 items by latent class. Responses regarding frequency of symptoms experienced in the previous two weeks were dichotomized into 0 = "Not at all" or 1 = "Several days", "More than half the days", and "Nearly every day". Counts per group are based on baseline response to PHQ-9.

PHQ-9 item	Never depressed (N = 275)	Energy/ sleep difficulties (N = 237)	Mild depression symptoms (N = 152)	Severe fluctuating depression (N = 88)
Little interest or pleasure in doing things	17 (6%)	55 (24%)	67 (45%)	57 (67%)
Feeling down, depressed or hopeless	8 (3%)	31 (13%)	45 (30%)	57 (66%)
Trouble falling asleep, staying asleep, or sleeping too much	39 (14%)	115 (49%)	93 (61%)	63 (73%)
Feeling tired or having little energy	55 (20%)	128 (55%)	116 (77%)	79 (92%)
Poor appetite or overeating	9 (3%)	32 (14%)	43 (28%)	38 (44%)
Feeling bad about yourself - or that you're a failure or have let yourself or your family down	6 (2%)	16 (7%)	34 (22%)	38 (44%)
Trouble concentrating on things, such as reading the news or watching television	15 (6%)	52 (22%)	70 (46%)	59 (69%)
Moving or speaking so slowly that other people could have noticed? Or so fidgety or restless that you have been moving a lot more than usual?	7 (3%)	12 (5%)	22 (15%)	32 (37%)
Thoughts that you would be better off dead, or thoughts of hurting yourself in some way?	1 (0%)	2 (1%)	10 (7%)	15 (17%)

maltreatment and late-life depression (Comijs et al., 2013). We add to these findings by demonstrating that older adults with any history of abuse were 3.5 times more likely to experience long term fluctuating severe depressive symptoms than the never-depressed group. We found that all four types of maltreatment were associated with severe fluctuating depression symptoms, and that psychological abuse and emotional neglect had the strongest effect. This is consistent with previous studies (Kim and Cicchetti, 2006; Liu et al., 2009), and a recent meta-analysis concluded that emotional abuse and neglect are risk factors for more severe, treatment-resistant depression with a chronic course (Nelson et al., 2017). In this study, only emotional neglect was associated with mild depression symptoms. Other studies have found physical abuse to have the strongest association with depression in older adults (Comijs et al., 2013). However, our study had a low prevalence of physical and sexual abuse, and therefore may not have had enough power to detect such an association.

We also found an association between lower morning cortisol levels and both energy/sleep difficulties and severe depression symptoms. While several previous studies also suggest that lower basal cortisol is associated with depression symptoms (Adam et al., 2017; Stetler and Miller, 2005), others have reported the opposite pattern of increased CAR with MDD (Dedovic and Ngiam, 2015; Rhebergen et al., 2015). Alternative explanations for these differences in findings, including that exposure to chronic stress early in life, leading to hypercortisolism in childhood and adolescence, may cause alterations in the feedback mechanisms of the HPA-axis leading to down-regulation and a subsequent flattening of the diurnal cortisol rhythm in adulthood (Raymond et al., 2018; Tarullo and Gunnar, 2006). Further research is needed to understand the effects of depression on basal cortisol levels, including additional studies assessing specific symptom types and courses.

We did not find an association between mild symptoms and morning cortisol levels, suggesting that this relationship may be related to an unobserved variable that has higher prevalence in the energy/sleep difficulties and severe classes. Possible alternative explanations for differences in cortisol profiles may include genetic predisposition and prenatal exposures (Di Iorio et al., 2017; Hunter et al., 2011; Tyrka et al., 2009). It is also possible that the severe fluctuating class represents a proposed etiologically-based subtype, "early trauma depression," which has been associated with low basal cortisol (Baumeister and Parker, 2012), as this class experienced the largest proportion of maltreatment. This is fitting with the hypothesis that victims of childhood maltreatment may experience hypercortisolemia in early in life, and this may decrease over time, leading to hypocortisolemia in later adulthood (Kuras et al., 2017; Trickett et al., 2010).

In addition, we found no differences between latent classes in evening cortisol, or cortisol measured after dexamethasone administration in the analysis including both men and women. Previous studies have found similar results (Rhebergen et al., 2015) with no differences in dexamethasone tests between older adults with and without depression disorders. Similarly, Vreeburg et al. (Vreeburg et al., 2013) found no associations between a worse depression course trajectory and cortisol suppression following dexamethasone administration or evening cortisol. However, another study (Carvalho Fernando et al., 2012) found that MDD patients demonstrated heightened cortisol before and after dexamethasone administration, and a correlation between increased cortisol levels and childhood maltreatment. However, when stratifying by sex, men with increased cortisol in the evening or after dexamethasone were more likely to experience mild depression symptoms, though this association was not statistically significant (Table S7).

We found no evidence of interaction between childhood maltreatment and cortisol levels. Additionally, when cortisol and maltreatment were adjusted for each other, we saw no significant change in effect size for either variable. These findings suggest that HPA-axis functioning, and maltreatment are independently related to depression symptom course. There are several potential explanations of the relationship between these three factors. Previous studies have found more recent life events may interact with AUCg or hair cortisol to predict depression symptoms (Schuler et al., 2017; Shapero et al., 2019). It is also possible that genetic (Normann and Buttenschon, 2019) or biological vulnerabilities may moderate the relationship between childhood maltreatment and depression. For example, previous studies indicate that an imbalance between glucocorticoid and mineralocorticoid receptors may mediate the relationship between childhood maltreatment and subsequent depression symptoms (Baes et al., 2014; Heim et al., 2008; Von Werne Baes et al., 2012).

One of the strengths of this study is the long follow-up period with many repeated measures of depression symptoms, to fully and accurately capture the long-term course of depression symptoms. Furthermore, this study included a large sample size with a high response rate. We were also able to measure cortisol levels over the course of the entire day, allowing measurement of different aspects of HPA-axis functioning, and assessed different types of childhood maltreatment.

There are also some limitations in this study, including the use of retrospective self-report questionnaires for childhood maltreatment, which could potentially lead to bias. It is possible that depressed individuals overreport prior negative experiences, whereas underreporting may be caused by memory problems, or an aversion to disclosing potentially painful or embarrassing prior experiences. In

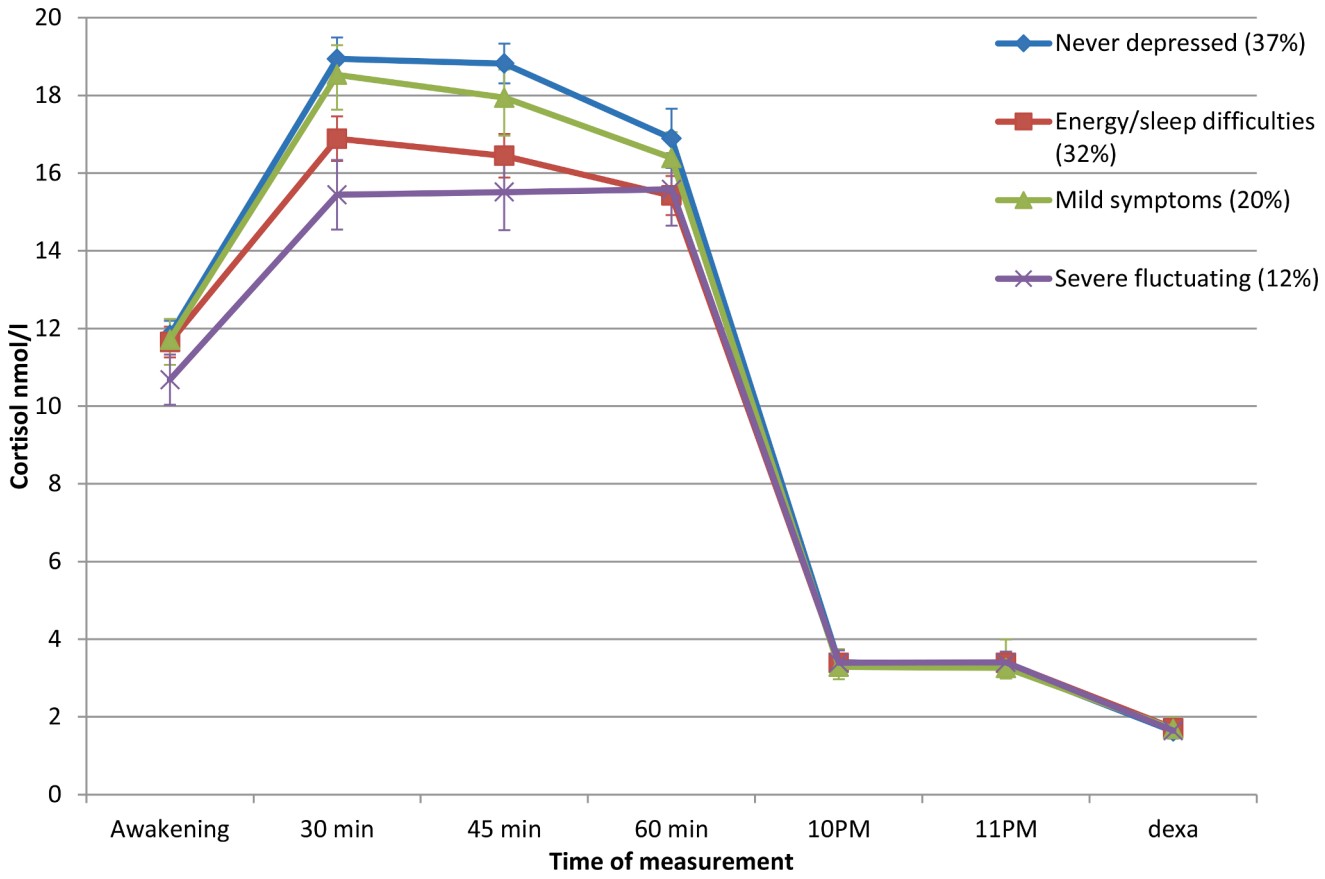

Figure 2. Diurnal cortisol curve stratified by depression class. Median cortisol levels by group measured in nmol/l at each time point with standard error bars.

addition, salivary cortisol was measured on one day, and multiple measurements would have increased reliability. However, this was not possible in such a large-scale study, though this limitation is mitigated by the large sample size of this study. Furthermore, cortisol can be influenced by a number of external factors. To investigate possible confounding from such factors, we ran models adjusted for a variety of somatic diseases, stress, smoking, and alcohol intake, which did not significantly alter effect sizes. Also, the study sample is highly homogenous; most participants were white males. Future studies should investigate the role of socioeconomic status and lower education in the relationship between childhood maltreatment and long-term course of depression in older adults, as these populations may differ in their risk of depression symptoms. This study also did not take any genetic predisposition into account, which could influence both depression and HPA-axis functioning. Future studies should take into account symptom profile as well as course, to assess if there are certain subtypes based on both the nature of the symptoms themselves and their stability over time. A more general study population, including subjects without cardiovascular disease, may increase the generalizability of these findings.

The relationship between childhood maltreatment and more severe depression symptoms supports the need for early intervention, as well as regular follow-up with older patients. It is evident from this study that childhood maltreatment has a persistent effect on depression symptoms even many years after the events transpire. The latent classes that experienced energy/sleep difficulties and mild depression demonstrate that many individuals with subclinical symptoms may never get a diagnosis or receive treatment, despite having these symptoms that may influence their quality of life. This also indicates the importance of a long-term follow-up, as it is possible that depending on the time of assessment, some participants could be diagnosed or not. Understanding these patterns over time may have implications for optimal treatment that could be missed in a cross-sectional approach.

Based on our findings, childhood maltreatment and blunted CAR are etiologic factors for a worse depression course. We also found that blunted morning cortisol may contribute to sub-clinical depression symptoms, specifically difficulties with energy levels and sleep. These findings in a large cohort with an extended follow-up period demonstrate that the effects of childhood maltreatment on depression symptoms continue into later life. The psychiatric and neurobiological consequences of early trauma are well-documented (Heim et al., 2010; Kaiser et al., 2018; Teicher et al., 2016), but it is important to develop further understanding of depression subtypes and specific symptomology in order to optimally treat victims of abuse and prevent lower quality of life as they age.

Funding

Financial support was received by the Alzheimer Nederland (Grant number WE.03-2017-06). The funding source had no involvement in writing of this article or the decision to submit it for publication.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Contributors

Morgan Scarth: Data analysis, preparation and editing of manuscript. **Jet Vonk:** advising on data analysis, editing and review of manuscript. **Lotte Gerritsen:** editing and review of manuscript. **Mirjam Geerlings:** supervision of data analysis and manuscript preparation, editing and review of manuscript. **UCC-SMART Study Group:** collection

Table 4
Models testing the associations between various cortisol measures or maltreatment variables and depression latent class. Odds ratios are calculated using the never depressed group as reference. Models are adjusted for age, sex, and education.

	Energy/sleep difficultiesvs. Never depressed OR (95% CI)	Mild depression symptoms vs. Never depressed OR (95% CI)	Fluctuating severeDepression vs. Never depressed OR (95% CI)
Model 2: Cortisol			
Awakening	0.99 (0.96-1.02)	0.99 (0.96-1.03)	0.96 (0.91-1.01)
30 minutes	0.98 (0.96-1.00)	0.99 (0.97-1.02)	0.94 (0.91-0.97)
45 minutes	0.98 (0.96-1.00)	0.99 (0.97-1.02)	0.96 (0.93-0.99)
60 minutes	0.97 (0.95-0.99)	0.98 (0.96-1.01)	0.97 (0.94-1.00)
Evening[†]	1.06 (0.75-1.51)	1.22 (0.81-1.82)	0.98 (0.58-1.68)
AUCg	0.97 (0.94-1.00)	0.99 (0.96-1.02)	0.93 (0.89-0.97)
AUCi	0.96 (0.93-1.00)	0.99 (0.95-1.03)	0.95 (0.91-1.00)
Dexamethasone	1.22 (0.88-1.69)	1.28 (0.88-1.86)	1.27 (0.79-2.05)
Rise	0.98 (0.95-1.00)	0.99 (0.97-1.02)	0.96 (0.92-0.99)
Model 3: Maltreatment			
Any abuse	1.28 (0.79-2.06)	1.95 (1.17-3.25)	3.50 (1.99-6.15)
Psychological	1.59 (0.79-3.19)	1.21 (0.54-2.75)	5.26 (2.55-10.86)
Emotional neglect	1.19 (0.65-2.18)	2.31 (1.25-4.26)	4.79 (2.53-9.07)
Physical	1.16 (0.55-2.42)	1.37 (0.62-3.04)	3.11 (1.43-6.76)
Sexual	1.57 (0.67-3.69)	1.53 (0.60-3.94)	2.78 (1.08-7.18)

Evening = average of 10PM and 11PM cortisol measurements
[†] =natural log transformed
AUCg= Area under the curve with respect to ground
AUCi= Area under the curve with respect to increase

and management of data.

Declaration of Competing Interest

The authors have no conflicts to disclose.

Acknowledgments

We gratefully acknowledge the contribution of the SMART research nurses; R. van Petersen (data-manager); B.G.F. Dinther (vascular manager) and the members of the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease-Study Group (UCC-SMART-Study Group): F.W. Asselbergs and H.M. Nathoe, Department of Cardiology; G. J. de Borst, Department of Vascular Surgery; M.L. Bots and M.I. Geerlings, Julius Center for health Sciences and Primary Care; M.H. Emmelot, Department of Geriatrics; P.A. de Jong and T. Leiner, Department of Radiology; A.T. Lely, Department of Obstetrics & Gynecology; N.P. van der Kaaij, Department of Cardiothoracic Surgery; L.J. Kappelle and Y.M. Ruigrok, Department of Neurology; M.C. Verhaar, Department of Nephrology, F.L.J. Visseren (chair) and J. Westerink, Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.12.036.

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