CHAPTER 2

ADVERSE CHILDHOOD AND RECENT NEGATIVE LIFE EVENTS: CONTRASTING ASSOCIATIONS WITH COGNITIVE DECLINE IN OLDER PERSONS

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ABSTRACT

Objective
To examine whether persons who experienced adverse childhood events or recent negative life events have a worse cognitive performance and faster cognitive decline, and the role of depression and ApoE-ε4 in this relationship.

Methods
The community-based sample consisted of 10-year follow up data of 1312 persons participating in the Longitudinal Aging Study Amsterdam (age range 65-85 years).

Results
Persons who experienced adverse childhood events showed a faster 10-year decline in processing speed but only when depressive symptoms were experienced. Persons with more recent negative life events showed slower processing speed at baseline but no faster decline.

Conclusions
Childhood adversity may cause biological or psychological vulnerability, which is associated with both depressive symptoms and cognitive decline in later life. The accumulation of recent negative life events did not affect cognitive functioning over a longer time period.
INTRODUCTION

Negative life events are common during the life course and may have adverse effects on cognitive functions, also in old age (1-4). These adverse effects may be caused by changes of the hypothalamic-pituitary-adrenal (HPA) axis. When stress is experienced glucocorticoids are secreted by the adrenal cortex, which can cross the blood-brain barrier, bind to specific receptors, and cause adverse changes to the (developing) brain. The hippocampus, amygdala, and frontal lobes are mainly affected by glucocorticoids, and longer periods of exposure to glucocorticoids may result in reversible dendritic alterations or permanent loss of neurons in the hippocampus, resulting in cognitive dysfunctions (3;5). It is suggested that especially when experienced in early childhood, adverse events may cause prolonged glucocorticoid exposure. Therefore differences in cognitive functioning may be detected even in late life (6;7). Adjacent to this biological pathway, psychosocial pathways may also lead to differences in late life cognitive functioning. Several studies observed adverse childhood conditions to affect education, occupation, lifestyle factors, and mental health, which in turn might be associated with decrements in cognitive functioning in late life (8-10).

Some studies focused on the association between childhood adversity and cognitive performance in older persons. Zhang et al. (11) observed worse cognitive performance in persons with adverse early life socioeconomic status. Fors et al. (12) observed a low social class of the father and conflicts in the family before the age of 16 to be associated with worse cognitive performance, and Ritchie et al. (13) observed the sharing of parental problems, mistreatment at school, loss of a parent, and movement to a foster home to be associated with worse cognitive performance. In addition, research in younger adult populations, observed (sexual) abuse to be associated with worse cognitive performance (14;15). Whereby a higher exposure was associated with worse cognitive performance (15-17). Richards & Wadsworth (18) observed early adverse circumstances to be associated with lower cognitive performance from childhood to middle age. However, there was little evidence for this association after middle age, and no evidence of a faster decline in cognition after middle age. Only few studies investigated the longitudinal association between adverse childhood events and cognitive decline in older persons. Ritchie et al. (13) reported verbal abuse and a father with an alcohol problem during childhood to be associated with a greater cognitive decline in late life. In addition, a favorable early environment was characterized by less decline, which was also observed by Zhang et al. (11). The follow-up of both studies was rather short: four and two years respectively. A longer follow up will give more information about the association between childhood events and cognitive decline.

Besides the association between childhood adversity and cognitive functioning, the experience of more recent negative life events might also have a negative effect on cognitive functioning.
Humans respond to stressful events with changes in cardiovascular, neural, autonomic, immune, and metabolic activity. This response serves an adaptive function, however, it may lead to allostatic load if the stress response is prolonged, as is the case in cumulative stress. This allostatic load reflects a ‘wear and tear’ on the body which is likely to play a role in the development of stress-related cognitive impairment (19). It may be expected that the experience of a higher number of stressful recent negative life events is related to a lower cognitive performance and faster cognitive decline due to the cumulating effect of stress. Some studies did not observe an overall effect of recent negative life events on cognitive decline (20;21), while others found a positive association between the number of recent negative life events and cognitive decline (1;22). In some studies specific associations were found for individual recent negative life events, some of which had a negative and others a positive effect on cognitive functioning (20;21;23-25). These inconsistent findings might be the result of differences in design, studies differed in sample characteristics, such as age, sex, and life event severity. In addition, some individuals might be more vulnerable to cognitive decline when stress is experienced than others. For example persons with already impaired cognitive functioning or a genetic predisposition for an increased risk in cognitive decline or unfavorable stress response. Next to this, not many studies have explored the longitudinal association between negative life events and cognitive functioning and few studies used relatively large study samples. Using large study samples results in higher variation and leading to less bias of the results. In the current study a large sample of older adults (n=1,312) with a follow up of 10 years will be examined. In addition, both information on adverse childhood events and recent negative life events was available. Therefore it was possible to test if the experience of adverse childhood events had an enduring effect on the association between recent life events and cognitive functioning in later life.

When investigating the association between life events and cognitive functioning, it is important to adjust for potential confounders. By testing a wide range of potential confounders more accurate associations might be observed. In addition, it is important to take mental health into account. The association between adverse childhood events or recent negative life events and late-life cognitive decline might depend on underlying depressive symptomatology. Thus, it seems important to consider the role of depression when studying the association between negative life events and cognition. For instance, Ward et al. (25) found an association between bereavement and poor cognitive performance, however, the poor affective state accounted for this effect. In contrast, a previous study from our research group showed that older persons who lost a spouse showed greater cognitive decline in memory function than those who remained married which was not mediated by the levels of depressive symptoms (24). In the current study information about depressive symptoms is available over 10 years of follow-up and it will be examined if depressive symptoms have a modifying effect on the association between recent life events and cognitive decline.
A genetic component, ApoE-ε4, might increase the vulnerability of the negative effects of stressful events on cognition, because this allele increases the risk for Alzheimer’s disease (26). A study in healthy adult women observed increased levels of self-reported stress to be associated with increased levels of depression but only in individuals with an ApoE-ε4 allele. Suggesting that ApoE-ε4-carriers have stronger responses to stress than non-ApoE-ε4 carriers (27). In addition, research suggests ApoE-ε4 to be a pleiotropic gene, whereby ApoE-ε4 might have cognitive benefits early in the life span and becomes a risk factor for cognitive impairment in late life (28). This might suggest that especially in later life ApoE-ε4 can be a vulnerability factor for cognitive impairment.

ApoE-ε4 has been shown to influence the association between adverse childhood and recent negative life events with cognition. Savitz et al. (17) observed sexual abuse in childhood to be associated with worse memory but only in ApoE-ε4 carriers. In addition, Ritchie et al. (13) observed positive childhood to be a protective factor but only in persons with non-ApoE-ε4. With respect to recent life events, in a former study we observed a stronger decline in global cognitive functioning after the death of a relative in ApoE-ε4 carriers than in non-carriers (20). This is in line with results of Peavy et al. (29) who observed worse memory in older persons with high chronic stress, based on life events and chronic difficulties, and at least one ApoE-ε4 allele compared to older persons with high chronic stress and no ApoE-ε4 allele. Thus it may be expected that the association between adverse life events and cognitive functioning is only present in ApoE-ε4 carriers.

In the present study we investigate the effects of adverse childhood events and recent negative life events on cognitive decline over a period of 10 years in older persons from a large community based sample. We expect that persons who experienced adverse childhood events have worse cognitive performance and a faster cognitive decline. Second, we expect that the cumulative effect of recent negative life events will have a negative effect on cognitive performance and cognitive decline. Third, to observe possible risk groups the modifying effect of depressive symptomatology and ApoE-ε4 was studied.

METHODS

Study sample
Data from the Longitudinal Aging Study Amsterdam (LASA), an ongoing population-based study, were used (30). The initial sample was recruited in 1992 in 11 municipalities in areas in the West, Northeast and the South of the Netherlands, thereby varying in religion and urbanization, with an oversampling of older people and older men in particular. Respondents were interviewed at their homes.
In 1992-1993 respondents were approached to participate in the first LASA cycle; 3,107 persons participated. Subsequently, respondents were approached for the following LASA cycles: the second cycle (1995-1996, n=2,545), the third cycle (1998-1999, n=2,076), the fourth cycle (2001-2002, n=1,691), the fifth cycle (2005-2006, n=1,275). Loss to follow-up was generally caused by death and to a lesser part by refusal and frailty. The procedures, population and non-response in LASA have been described in more detail in Huisman et al. (31).

In the present study, we selected the older age-group (≥ 65 years) from the second cycle (n=1,576) because cognitive decline is most prevalent in this age group, furthermore, from this group we had multiple cognitive measurements and information about life events. Respondents were included when at least two measurements of cognitive functioning were available and information on adverse childhood events or two measurements of recent negative life events, resulting in a total sample of 1,312 persons. Respondents who were excluded (n=264) were older, more often male, had lower scores on cognitive measures at baseline, and experienced less often adverse childhood events (p<0.05). Separate analyses were performed for adverse childhood events and recent negative life events for each cognitive measure, resulting in small sample differences across analyses.

Measures

Cognition

Processing speed was measured using the coding task. In LASA, an adjusted version of the letter substitution task, the Alphabet coding Task-15 (32) was used. Two rows of 15 combinations of characters were shown, each character in the upper row belonged to a character in the bottom row. The test contained one upper row with characters and an empty lower row. The respondent had to complete as many character combinations as possible, by naming the corresponding character using the substitution key. This was done in three cycles of one minute and the maximum score of the three trials was used in the analyses.

Memory was tested with the 15-word test, a Dutch version of the Auditory Verbal Learning Test (33). We used three instead of five learning trials to reduce burden for the respondent. After every trial the respondent had to recall as many words as possible and after a distraction period of 20 minutes the respondent was asked to name the words learned before again. The number of words recalled after the distraction period were counted as the delayed recall score. To reduce a possible practice effect, parallel versions of the 15 words test were alternated in follow-up measurements.
General cognitive functioning was assessed with the Mini-Mental State Examination (MMSE) (34). The MMSE is a widely used instrument used for screening of cognitive impairment. It consists of 20 items and the scores range from 0-30 with a higher score indicating better cognitive performance. Questions concern the following cognitive domains: orientation in time, place, attention, calculation, immediate and delayed recall, language, and visual construction.

Adverse childhood events
At baseline persons were asked with an open-ended question if they had experienced any significant life events before the age of 18 years which had a lasting impact on the rest of their life. The reported adverse childhood events were categorized in the following categories: war experiences (n=65), death of a parent (n=53), death of an important other (n=32), excessive alcohol use of close relative (n=9), sexual abuse (n=6), severe problems at home (n=72), poverty or unemployment of parents (n=7), physical illness of respondent (n=21), and other problems (n=87). A dichotomous variable was made categorizing respondents in having or not having experienced a significant adverse life event during childhood.

Recent negative life events
Respondents were asked which negative life events were experienced in the previous three years, the period between the current and the previous interview. The questions were adapted from the life event inventory developed by Tennant & Andrews (35) with the aim of assessing the stress of life events. The items used in the LASA data collection were selected on the following criteria: the event is likely to occur relatively frequently in the older population, and the event scores relatively highly on the distress and life changes scales (36). The following stressful life events (with the numbers at baseline) were assessed: death/divorce of partner (n=95), death of a close relative (n=360), death of a (grand)child (n=40), illness of partner (n=175), illness of relatives (n=576), serious conflict with others (n=99), and being a victim of crime (n=41). The sum of the total number of negative life events experienced after the previous interview was counted at each next cycle.

Potential confounders
The following variables were considered as possible confounders: age, education, gender, alcohol intake, smoking status, cardiovascular disease, diabetes mellitus, and hypertension.

Information on age and gender were derived from the population registries. Education was assessed at baseline by asking the highest educational level that was completed and recoded to number of years of education (range: 5-18 years). Alcohol intake was asked by the number of alcoholic units consumed per week, and was thereafter classified as no,
middle, and high consumption according to the Netherlands Economic Institute (NEI) index (37). Smoking status was classified as never, former, and current. Cardiovascular diseases (angina pectoris, myocardial infarction, congestive heart failure, cardiac arrhythmia, peripheral arterial disease, and cerebrovascular accident) were based on self-report, family and physician records, and medication use (38). Diabetes was based on self-report, family and physician records, and the use of antidiabetics. Hypertension was defined as a systolic blood pressure of 160 mm/Hg or higher and/or a diastolic blood pressure of 100 mm/Hg or higher and/or anti-hypertensive medication use. Information on alcohol intake, smoking status, cardiovascular disease, diabetes mellitus, and hypertension were obtained at all four cycles.

Potential modifiers

Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale (CES-D) (39). The scale consists of 20 items covering depressive symptomatology experienced in the past week. Each answer was rated on a 4-point scale ranging from 0 ‘rarely never’ to 3 ‘mostly or always’. The maximum score was 60 points. The CES-D was assessed at each measurement. The psychometric properties of the Dutch version were validated in older persons (40).

At baseline serum samples were obtained and frozen at -80 degrees until determination of Apolipoprotein E (ApoE). The ApoE phenotypes were determined by isoelectric focusing of delipidated serum samples, following by immunoblotting (41). ApoE status was classified as ApoE-ε4 carriers for respondents with the ApoE-ε4 isoform (phenotypes ε2/4, ε3/4, ε4/4) and as non-ε4 for respondents without the ApoE-ε4 isoform (phenotypes ε2/2, ε2/3, ε3/3).

Statistical analyses

The MMSE score was transformed ln(31-MMSE score) to obtain a near-normal distribution (42). The other cognitive measures showed a normal distribution. To study the association between adverse childhood events or recent negative life events and cognitive decline, random coefficient analyses were performed using Linear Mixed Models (LMM) in SPSS for windows, version 20.0 (IBM Corporation, 2011, Armonk, NY). With LMM, regression analyses can be performed with repeated measures data. This method takes into account the dependency of the repeated observations from the same individual over time. A major advantage of LMM is that the respondents are included regardless of missing values; this reduces the bias of differential loss to follow-up of the more cognitively impaired participants. In the present study, a random effect of time with covariance structure ‘unstructured’ was included. We started with a model including adverse childhood events, time (i.e. 0, 3, 6, and 10 years) and the interaction of adverse childhood events*time because we were also
interested in the association with cognitive decline. A random intercept (subjects) was included, taking into account different intercepts for different persons. Next, a random slope for time was entered into the models, if the maximum likelihood of the model including the random slope was significantly better we kept the random slope in the model. Possible confounders were added separately to the model, the confounder with the highest percentage change (at least 10%) on the regression coefficient of childhood events on cognitive functioning was kept in the model. Then the remaining confounders were added to the model and the strongest confounder was also kept in the model. This procedure was repeated until the percentage change was below <10%. The continuous confounders age and education were centered on the round up mean of 75 years of age and 9 years of education to improve interpretability of the models. The unstandardized regression coefficient of adverse childhood events reflects the association between adverse childhood events and cognitive performance at baseline. The unstandardized regression coefficient of the interaction term reflects the association between adverse childhood events and cognitive decline. Thereafter, to investigate if the rate of cognitive decline was stronger in persons with depressive symptoms and in ApoE-ε4 carriers (yes, no), three-way interaction terms with adverse childhood events were added separately to the fully adjusted models (adverse childhood events x time x depressive symptoms or adverse childhood events x time x ApoE-ε4). Interaction-terms were considered significant when the p-value of the interaction term was below 0.10 (43).

Next, the association between recent negative life events during 10 years of follow-up and cognitive decline in this same period was examined. The same procedures described for adverse childhood events were used to examine this association. In addition, to examine whether the experience of adverse childhood events influenced the association between recent negative life events and cognitive decline, three-way interaction terms between recent negative life events, childhood events, and time were entered to the fully adjusted models.

RESULTS

First, the characteristics of the study sample were described (Table 1). The mean age of the study sample was 75.2 (SD=6.42) years at baseline and 82.8 (SD=5.54) years after 10 years of follow-up. 27.1% of the study sample experienced an adverse event during childhood. The mean number of recent negative life events remained relatively stable over these 10 years; about 70% of the older persons experienced at least 1 recent life event at each cycle.
Table 2 shows the association between adverse childhood events and cognition over 10 years of follow-up examined with linear mixed models. In the comparisons of the maximum likelihoods of the models with and without random slopes for time, all models showed significantly better maximum likelihoods including the random slope. Therefore the random slope for time was kept in all models. Regarding cognitive measures, the mean scores on processing speed, delayed recall, and ln transformed MMSE decreased over time as seen by the time factor (B=-0.46; -0.18; 0.03; all p<0.001).

There was a negative association between adverse childhood events and processing speed, indicating that persons who experienced adverse childhood events showed a slower
processing speed at baseline. However, this association did not reach significance (B=-0.64, p=0.12). Over time persons who experienced adverse childhood events showed a less fast decline on processing speed and delayed recall, which is shown in marginally significant interaction terms (adverse childhood events*time: B=0.08, p=0.06 vs. B=0.04, p=0.06).

Next, we investigated whether the associations between adverse childhood events and cognitive decline was modified by depression or ApoE-ε4. Depression showed a modifying effect between adverse childhood events and processing speed over time (interaction term adverse childhood events*time*depression: p=0.01). Figure 1 suggests that persons with adverse childhood events and depression (CESD cut-off ≥16), had a stronger decline in processing speed compared to persons with adverse childhood events and no depression (interaction term: p=0.073). In addition, in non-depressed persons with adverse childhood events a less fast decline was observed compared to non-depressed persons without childhood events (interaction term: p=0.007). Moreover, persons with depression and no childhood events were slowest on processing speed but may not show a faster rate of decline compared to persons with depression and childhood events. No significant interaction effects were found for persons with and without ApoE-ε4.

**Effect of recent negative life events on cognition**

The association between the number of recent negative life events and cognitive decline was also examined by means of linear mixed models (Table 3). We found a negative association between the number of recent negative life events and processing speed (B=-0.30, p=0.01). This indicates that at baseline the mean processing speed was slower for persons who experienced more recent negative life events. Additionally, we found that the rate of decline in processing speed was slower for persons who experienced recent negative life events (B=0.05, p=0.02). No significant associations were found between recent negative life events and delayed recall and global cognitive functioning.

Next, we investigated the effects of depression and ApoE-ε4 on the association between recent negative life events and cognitive decline. No significant interaction effects were found for persons with and without depression and for persons with or without ApoE-ε4. In addition, the three-way interaction terms between recent negative life events, adverse childhood events and time were not significant on any of the cognitive domains.
Table 2. The association between adverse childhood events and cognitive functioning over 10 years of follow-up.

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Abbreviations: MMSE, Mini-Mental State Examination; ApoE, apolipoprotein E.

*Adjusted for age and education.

*Adjusted for age.

*Adjusted for age, education and smoking status.
DISCUSSION

In the present study we investigated the effects of adverse childhood events and recent negative life events on performance and decline in processing speed, delayed recall and global cognitive functioning in older persons from a large community based sample over a period of 10 years. In our study sample of 1,312 older persons, 27% experienced adverse childhood events, and about 70% experienced at least one recent negative life event in every three-year period. Associations were found between both adverse childhood events and recent negative life events with information processing speed. In persons with adverse childhood events we found a faster rate of decline in processing speed but this may only be present in persons with depressive symptoms. Persons who experienced more recent negative life events showed a slower information processing speed at baseline, but no faster decline.

A worse cognitive performance in persons with adverse childhood events was observed in previous studies (11-13). An explanation for worse performance might be that the stress associated with adverse childhood events causes changes in the HPA-axis, resulting in high levels of glucocorticoids affecting the hippocampus, which is highly vulnerable to stress because of a high density of glucocorticoid receptors (6). In addition, the corpus callosum, which plays a crucial role in hemispheric integration and thereby information processing is affected by high levels of stress hormones and may cause the slower processing speed.
Table 3. The association between recent negative life events and cognitive functioning over 10 years of follow-up.

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<th>Adjusted model for significant confounders</th>
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<td>-0.07</td>
<td>0.003</td>
<td>0.01</td>
</tr>
<tr>
<td>- depression*time</td>
<td>-0.002</td>
<td>0.57</td>
<td>-0.003</td>
</tr>
<tr>
<td>- recent negative life events*time</td>
<td>0.04</td>
<td>0.23</td>
<td>-0.01</td>
</tr>
<tr>
<td>- recent negative life events*depression</td>
<td>0.02</td>
<td>0.23</td>
<td>-0.01</td>
</tr>
<tr>
<td>- recent negative life events<em>time</em>depression</td>
<td>0.001</td>
<td>0.66</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Adj usted model with interaction recent negative life events<em>time</em>ApoE-ε4</strong></td>
<td></td>
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<tr>
<td>- intercept</td>
<td>26.77</td>
<td>5.00</td>
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</tr>
<tr>
<td>- recent negative life events</td>
<td>-0.39</td>
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</tr>
<tr>
<td>- time</td>
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<td>&lt;0.001</td>
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<tr>
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<td>0.28</td>
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<tr>
<td>- recent negative life events<em>time</em>ApoE-ε4</td>
<td>-0.03</td>
<td>0.53</td>
<td>0.03</td>
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</table>

Abbreviations: MMSE, Mini-Mental State Examination; ApoE, apolipoprotein E.

\(^a\)No significant confounders.
\(^b\)Adjusted for age, sex, education.
\(^c\)Adjusted for education, hypertension, cardiovascular diseases, and alcohol consumption.
observed in persons experiencing adverse childhood events (6). Another explanation might be that adverse childhood events lead to lower cognitive performance through disadvantages in education and social economic class following adverse childhood events (18). However, in studies that were able to address this effect, it was mostly small, in contrast to the direct effects of the prolonged exposure to stress in childhood (11;12). Moreover, in our study we did not observe differences in education level, occupation prestige, and receiving emotional support between persons with and without adverse childhood events. Therefore, we think educational or occupational disadvantages and diminished emotional support might not explain the association between childhood events and late life cognitive functioning in this study.

Our results seem to point to the idea that adverse childhood events may lead to a faster rate of decline in processing speed in individuals with depressive symptoms. In an earlier study from our group we showed that adverse childhood events were associated with depressive symptoms in later life (44), and we also previously showed that depression in late life was associated with slower speed of information processing (45;46). Persons who experienced childhood events but no depressive symptoms might have better levels of resilience after the experience of childhood events, potentially because of good coping strategies and might therefore not present with depressive symptoms and faster cognitive decline. An unexpected finding was that persons with depression but no adverse childhood events showed the worst cognitive functioning over 10 years. An explanation might be that aspects of resilience that some people retain after the experience of childhood adversity might not be present. Persons who only experience depression might therefore have less effective coping strategies, which might lead to worse cognitive functioning.

We found that the experience of recent negative life events was associated with a slower information processing speed. Although some studies did not find this association (21), this is in agreement with other previous research, suggesting that the experience of a higher number of stressful recent negative life events is related to lower cognitive performance due to the cumulating effect of stress (1;22). However, we found less cognitive decline in persons experiencing more recent negative life events. In the study by Peavy et al. (47) a faster cognitive decline was associated with chronic stress but only in older adults with mild cognitive impairment. It might be that stressful negative life events only have a negative effect on cognitive decline in more vulnerable persons with already diminished cognitive abilities. This was not examined in our study because we did not have a formal diagnosis of mild cognitive impairment. However, there was no indication of a different association in persons with poor cognitive functioning because no different associations were observed between persons with a MMSE≤24 versus a MMSE>24 (results not shown).
Another possible explanation might be that experiencing more life events has a direct negative effect on cognitive functioning but this effect may be reversible when the stressors are no longer present and therefore no decline in cognitive functioning might be observed over a longer time period. This is in agreement with a former study of our research group in which no faster cognitive decline was observed after the experience of an airplane crash (48). It might also be that mortality selection contributed to the finding of less cognitive decline in persons experiencing more recent life events. However, no higher mortality was observed in persons experiencing more recent life events and adjustment for mortality selection using the method described by Liu (49) did not change the results.

In the current study we did not find any modifying effects for ApoE-ε4 for both adverse childhood events and recent negative life events. This is in contrast with Savitz et al. (17) who observed sexual abuse in childhood to be associated with worse memory in middle aged adults but only in ApoE-ε4 carriers. Unfortunately we had not enough power to test this association in persons reporting sexual abuse specifically. Moreover, Ritchie et al. (13) did not observe a gene-event interaction between ApoE-ε4 and adverse childhood events but found positive childhood to be a protective factor but only in persons with non-ApoE-ε4. With respect to recent life events, in an earlier study we observed a stronger decline in global cognitive functioning after the death of a relative in ApoE-ε4 carriers than in non-carriers (20). This is in line with results of Peavy et al. (29) who observed worse memory in older persons with high chronic stress and at least one ApoE-ε4 allele compared to older persons with high chronic stress and no ApoE-ε4 allele. However, earlier research was on specific events and not on the cumulating effect of stressful life events.

Although depressive symptoms are associated with poorer cognitive functioning, we found no support for the assumption that the relation between recent life events and cognitive functioning could be explained by depressive symptoms. This is in line with some previous research (20;23;24) but not with other research. Ward et al. (25) found an association between bereavement and poor cognitive performance, but the poor affective state accounted for this effect. However, these studies were based on single recent negative life events and mainly loss of a partner. In addition the study by Ward et al. (25) used a cross-sectional design and a small sample size (n=50). Recent life events are closely related to the life phase wherein people live, persons experiencing life events at a higher age might adjust faster to the recent life events because of previous experiences and learned coping strategies (50). Therefore, the effects of recent life events might be shorter, and lead to less overall stress, depression and cognitive dysfunctioning than childhood events. Other mechanisms may underlie the association between recent life events and cognitive functioning, such as effective coping strategies and psychological resilience. In addition, the amount of stress,
if small, might also have an arousing effect, which might be an explanation for no faster cognitive decline in association with recent negative events (20;21).

In our study, both adverse childhood events and recent negative life events were associated with a slower speed of information processing. Speed of information processing might be the most sensitive measure used, and might show the earliest decline compared to the other cognitive measures. We did not find an association between adverse childhood events and recent negative life events and global cognitive functioning measured with the MMSE. The MMSE may be too global to observe subtle differences, moreover our study sample might be too young and ‘cognitive healthy’ to detect relevant differences on the MMSE. In the study by Zhang et al. (11) an older age group (80-105 years) was studied and a lower score on the MMSE was observed when adverse childhood conditions were experienced.

Some limitations of this study must be mentioned. First, both adverse childhood events and recent negative life events were based on retrospective self-reports. This might have led to underreporting due to memory impairment, however, MMSE scores were in the normal ranges so therefore underreporting due to memory impairments is unlikely. In addition, it is likely that some adverse childhood events were not reported because of embarrassment or painful thoughts. This might have led to underreporting of especially traumatic events, which could cause underestimation of associations between adverse childhood events and cognitive functioning. Alternatively, persons who experienced more mood problems later in life might have responded more positively to the question if childhood adversity had an impact on the rest of their lives, which might have resulted in an overestimation of the associations between childhood events, depressive symptoms and cognitive functioning. Second, we do not know if persons experienced multiple childhood events because only one type of event could be given. Although persons reported the most severe type of childhood event, the categories might not be mutually exclusive. To get an idea of the effect of differential categories on cognitive functioning, exploratory analyses were performed on serious war experiences, loss of parent, loss of intimate, severe problems at home and other problems at home because these events were reported by enough persons to perform additional analyses (n>20). Although interpretation of these results should be done with appropriate cautiousness, the effect of childhood events on cognitive functioning seemed to be mainly driven by serious war experiences. Third, in the LASA cohort, attrition was mainly attributed to mortality (31), and because of mortality, but also refusal, and exclusion criteria the frailest older people were excluded in the analyses, which might have led to underestimation of the associations. Fourth, we had no information about the level of stress associated with the adverse childhood events and recent negative life events and cannot be sure that the events were experienced as stressful. It remains an issue to use the simple sum
of life events or a weighted score in which certain life events are considered more important than others. When we would use a weighted score, according to the weights provided by Tennant and Andrews (35), our results showed very similar results (e.g. confirmed the impact of life events on processing speed). Unfortunately no information about negative events in midlife was collected so no results about cumulative stress during the life span could be given. Future research should study the level of stress associated with life events, including duration and intensity. In addition, other mechanisms beside depressive symptoms might be of interest in the association between life event stress and cognitive functioning. Possible psychological pathways might be intrusive thinking, such as ruminative thinking and worrying, but also sleep problems and coping strategies.

The current study also has some major strengths. A large sample of older persons was included, and a wide range of confounding variables was available. In addition, 10-year longitudinal data on different cognitive domains, depressive state, and recent negative life events were available, and both adverse childhood events and recent negative life events could be investigated.

In conclusion, adverse events experienced in childhood and recent negative life events influence cognitive functioning in later life. However, different mechanisms may underlie these associations. Whereas, recent life events may only have a short term negative effect on cognitive functioning, the stress associated with the experience of adverse childhood events may cause a biological or psychological vulnerability which is associated with both depressive symptoms and cognitive decline in later life. The experience of only adverse childhood events but no symptoms of depression may not lead to a faster cognitive decline potentially because of better resilience in those individuals.
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