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ADVERSE CHILDHOOD ENVIRONMENT AND LATE-LIFE COGNITIVE FUNCTIONING

Karen Ritchie^{1*§}, Isabelle Jaussent^{1§*}, Robert Stewart^{1,2}, Anne-Marie Dupuy^{1,3}, Philippe Courtet^{1,4}, Alain Malafosse^{1,5}, Marie-Laure Ancelin¹.

*Joint first authors

RUNNING HEAD: Adverse childhood environment and late-life cognitive functioning

¹Inserm, U888, Montpellier, F-34093 France ; Univ Montpellier 1, Montpellier, F-34000 France ;

²King's College London (Institute of Psychiatry), De Crespigny Park, London, SE5 8AF, United Kingdom ;

³Laboratoire de Biochimie, Hôpital Lapeyronie, CHU Montpellier, Montpellier, F-34295 France ;

⁴Service de Psychologie Médicale et Psychiatrie, CHU Montpellier, F-34000, France ;

⁵University Hospital and School of Medicine of Geneva, University of Geneva, Switzerland.

§corresponding author:

Inserm U888 Pathologies of the Nervous System

La Colombière Hospital,

39 Avenue Flahault, BP 34493, 34093 Montpellier Cedex 5, France

isabelle.jaussent@inserm.fr

Tel: (33) 4 99 61 45 60; Fax: (33) 4 99 61 45 79

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SUMMARY

Objective: Clinical studies suggest that childhood maltreatment may cause nervous system changes and consequent cognitive disorder. The persistence of this association in late-life is examined.

Methods: Cognitive functioning and childhood events were examined in 1282 persons over 65 years, taking into account proximal competing causes of poor cognitive performance.

Results: 91 % of participants experienced at least one adverse childhood event, of these 14.7 % severe events. Sharing of parental problems and, for women, loss of a parent, were associated with poorer verbal retrieval whereas being sent to a foster home or mistreatment by schoolmates was associated with poorer visuospatial memory. Severe abuse was associated with a lower risk of cognitive impairment on some tests suggesting a resilience factor. Positive childhood environment was protective although only for non-carriers of the ApoE $\epsilon 4$ allele on the central executive task.

Conclusions: Some adverse childhood events continue to have a negative effect on later-life cognitive performance, while some more severe acute events may have the opposite effect, underlying the necessity to consider events individually and not as global test scores.

INTRODUCTION

Childhood maltreatment has been observed to induce both structural and functional brain changes, notably reduced development of the hippocampus and amygdala, and abnormal fronto-temporal electrical activity (Teicher *et al.*, 2002; Teicher *et al.*, 2003). Not surprisingly these changes have a significant detrimental effect on cognitive functioning. Clinical studies show that children subject to abuse without neurological injury show deficits of central executive functioning, memory, attention, visuospatial ability, language and motor speed, in some cases also accompanied by significant cerebral atrophy (Prasad *et al.*, 2005; Savitz *et al.*, 2007; Pears and Fisher, 2005; Nolin and Ethier, 2007; Porter *et al.*, 2005). Abuse has also been associated with lower IQ (Koenen *et al.*, 2003; Nolin and Ethier, 2007). While the greatest cognitive deficits are observed in cases of physical abuse with neglect, neglect alone has been associated with cognitive deficits in attention, response set and visual-motor integration, and conversely greater capacity for problem solving and abstraction (Nolin and Ethier, 2007; Pears and Fisher, 2005). There is furthermore some early evidence from a study of childhood abuse and cognition in bipolar disorder of a gene-environment interaction implicating genes known to exert a neurotrophic effect in response to cellular injury (Savitz *et al.*, 2007) notably Apolipoprotein E (ApoE), which has also been linked to late-life cognitive functioning and dementia (Blacker *et al.*, 2007; Caselli *et al.*, 2007). Polymorphisms on the ApoE gene are believed to influence capacity for compensatory neurite outgrowth and synaptogenesis following neuronal injury (Poirier, 1994) and may thus modulate the neurobiological impact of environmental trauma.

There is some evidence for the persistence of the cognitive consequences of child abuse into adulthood. Several small clinical studies of women with a history of physical and sexual abuse reported disorders of vigilance, memory and mathematical ability compared to controls (Navalta *et al.*, 2006; Bremner *et al.*, 1995; Bremner *et al.*, 2004) but with no impact on IQ.

Although Stein et al. found no significant impairment on a verbal and visual recall task in 22 adult women subject to childhood sexual abuse (Stein *et al.*, 1999), they did observe significantly reduced left-side hippocampal volume (Stein *et al.*, 1997). Little is known, however, about the longer-term impact of abuse-related brain changes, and in particular whether they may constitute a significant risk factor for cognitive disorder in old age. While adverse life events occurring in old age have been related to poorer cognitive performance, the impact of more distal trauma, notably those occurring at critical stages of brain development, has yet to be explored.

This study aimed to examine the relationship between childhood trauma and late-life cognitive performance in an elderly general population, taking into account proximal risk factors for poor cognitive performance, and interaction with ApoE genotype. We considered the possibility that childhood abuse would engender damage to developing cortical structures which would persist into adulthood and we hypothesised that it would be associated with lower late-life cognitive functioning when neuronal resources are again challenged. The prospective study design allowed us to compare both levels of cognitive functioning and decline over a four-year period. We further hypothesized that the extent of cognitive compromise will be modified by genetically determined capacity for neuronal repair.

METHODS

Sample

Community dwelling persons, 65 years and over, were recruited by random selection from the fifteen electoral roles of the Montpellier district between March 1999 and February 2001 as part of the ESPRIT study of late-life psychiatric disorder (Ritchie *et al.*, 2004). Participants were given a base-line examination and re-examined on two further occasions at two-yearly

intervals. At follow-up the neurological, cognitive and psychiatric examinations were repeated and medication use and incident illness were recorded. The present analyses have been carried out on participants who completed the child abuse questionnaire, who did not have dementia at base-line or follow-up (due to doubts about the reliability of the information given about childhood events) and for whom information was available on all potential confounding variables (1282 of 1580 subjects). Ethical approval for the study was obtained from the National Ethics Committee.

Measures

Participants were asked to attend a half-day examination by a neurologist and a centre interviewer (nurse or psychologist) at the Neurology Hospital. Disabled subjects unable to come to the study centre were interviewed in their homes. The following procedures were carried out:

A standardized health interview covering present state of health, individual and family medical history, and medication use (subjects were asked to bring their medication to the centre). Recent exposure to adverse life events in the past year was assessed using the Gospel Oak questionnaire (Harwood *et al.*, 1998). Detailed medical questionnaires were used to obtain information on history of vascular disease (including angina pectoris, arrhythmia, lower limb arteritis, heart failure, myocardial infarction, stroke), other chronic illnesses (asthma, diabetes defined as fasting glucose ≥ 7.2 mmol/l or reported treatment, hypercholesterolemia defined as total cholesterol ≥ 6.2 mmol/l or reported treatment, hypertension defined as resting blood pressure $\geq 160/95$ mm Hg or treatment, and thyroid disorders). Participants with chronic diseases were classified as having one, or two or more, of these illnesses.

A standardized neurological examination based on ICD-10 criteria (WHO, 1992) was carried out to detect neurological and cardiovascular co-morbidity, including measures of sitting and standing blood pressure.

A standardized psychiatric interview to record life-time and current DSM-IV Axis I psychiatric disorder; the Mini International Neuropsychiatric Interview (MINI) (Lecrubier *et al.*, 1997) (French version 5.00) previously validated within the general population setting. Positive cases were reviewed by a panel of psychiatrists. The Center for Epidemiologic Studies-Depression Scale (CES-D) (Radloff, 1977) was used to detect high levels of depressive symptomatology.

Childhood environment A self-administered checklist based on a review of existing instruments covering 25 adverse and 8 protective factors (expressed as categorized variables, yes/no) was given to subjects for completion in the third wave of the study (four years after recruitment) as described previously (Ritchie *et al.*, 2009) Adverse factors (traumatic events) included physical, verbal and sexual abuse, conflict at home, mental cruelty, neglect, mental disorder in parents, excessive sharing of parental problems, separation, illness, poverty, mistreatment at school, separation, war and natural catastrophe. Protective factors included maternal and paternal affection, availability of an adult friend, impression of having had a happy childhood or a normal education, parents perceived as doing their best, feeling happy at school, having been raised by both parents.

Cognitive functioning. The Benton's Visual Retention Test assessed visual memory (Benton, 1965), the Trail Making Test B (TMTB) assessed executive function respectively (Reitan, 1965), the Isaacs' Set Test measured verbal fluency (Isaacs and Kennie, 1973) and the 5-word test of Dubois examined immediate and delayed verbal memory (Dubois, 2001). The National Adult Reading Test (NART) (Blair and Spreen, 1989) was used as a marker of IQ and was administrated as baseline.

Diagnosis of dementia. A preliminary diagnosis and classification of dementia at each follow-up was made by the study clinical investigators, according to DSM-IV revised criteria (APA., 1994) and was further validated by a national panel of neurologists independently of the investigators.

Blood samples were taken at base-line to establish ApoE genotype (Dufouil *et al.*, 2005).

Statistical Analysis

Two-tailed chi-squared tests were used to determine which of the baseline characteristics were significantly associated with poor performance on each of the cognitive tasks. Univariate logistic regression analyses adjusted for age, sex, and educational level were used to determine if childhood events were significantly associated with cognitive impairment (cross-sectional analysis) or cognitive decline (longitudinal analysis). Adjustment on baseline cognitive score was also performed for the analysis of cognitive decline. Multivariate adjusted logistic regression included covariates that were associated with poor cognitive performance ($p \leq 0.10$). Cognitive impairment was defined as being in the lowest quartile of the baseline cognitive score for the Isaacs, Benton and Dubois tests and in the highest quartile for TMTB. Cognitive decline was defined as being in the lowest quartile of the maximal difference between baseline score and either follow-up.

We tested the hypothesis that ApoE genotype might modify the relationship between cognitive impairment or decline and childhood events using a logistic regression model. We therefore stratified our analysis by ApoE genotype and then added the interaction term to the full model and tested for its significance using Wald's χ^2 test given by the logistic regression model. The distribution of ApoE was tested by χ^2 for Hardy-Weinberg equilibrium.

Significance level was set at $p < 0.05$. The statistical analysis was carried out using SAS software (version 9.1).

RESULTS

Ninety one percent of participants experienced at least one adverse childhood event and of these 14.7 % reported at least one traumatic childhood event (physical, verbal or sexual abuse, neglect, excessive punishment, humiliation). Comparing this latter group to subjects without a severe event, who also recalled their childhood as being generally happy, no significant difference was found in relation to NART scores. Twenty nine percent of subjects who experienced traumatic events were classified as having Mild Cognitive Disorder according to commonly accepted criteria (Petersen *et al.*, 2001) compared to 24% of subjects with happy childhood, although this difference did not reach statistical significance. The principal socio-demographic and clinical characteristics of the population are given in **Table 1**. As expected a significant relationship was found on all cognitive tests with age, education and IQ. Reporting recent life events was not associated with modified performance on any cognitive test. Chronic disorder and sex were associated with cognitive performance on all tasks except the Benton. Performance on the Isaac test was also marginally associated with depression, the Benton test with depression and marginally with widowhood, TMTB with widowhood, ApoE4, and depression.

The association between individual childhood events, both protective and adverse, and late-life cognitive performance was then examined in relation to each test adjusting for potential confounders. Significant associations are given in **Table 2**. On the Isaacs test, sharing of parental problems with the children in the family (OR=1.68; 95%CI=1.18-2.38, p=0.004) and parental loss (OR=1.43; 95%CI=1.03-2.00, p=0.035) were found to constitute significant risk factors for poor performance in later-life. Being sent to a foster home (OR=2.23; 95%CI=0.96-5.15, p=0.062) or having been mistreated by schoolmates (OR=2.27; 95%CI=0.98-5.29, p=0.057) are marginally risk factors for poor performance on the Benton test. Parents being perceived as having done their best in relation to their children tends to be

a protective factor for performance on both the Dubois (OR=0.63; 95% CI =0.38-1.04, p=0.074) and TMTB (OR=0.61; 95%CI=0.36-1.02, p=0.062), with perceptions of a happy childhood also being associated with better scores on the TMTB (OR=0.64, 95%CI=0.41-1.00, p=0.051). Reporting a normal education was also associated with better scores on the Benton (OR= 0.60; 95%CI=0.34-1.05, p=0.072) and TMTB (OR=0.56; 95%CI=0.33-0.94, p=0.029). Experiencing physical, mental or sexual abuse was associated with a lower risk of cognitive impairment on the Isaacs test, however small numbers make separate analyses for each type of traumatic event unreliable. Having had a mother suffering from mental problems was associated with a lower risk of cognitive impairment on the Dubois (OR=0.61; 95%CI=0.39-0.95, p=0.035) and Benton tests (OR=0.60; 95%CI=0.36-1.01, p=0.056).

The distribution of ApoE did not deviate from Hardy-Weinberg equilibrium ($\chi^2=1.21$, df=5, p=0.94). Gene-event interactions were found between happy childhood and ApoE polymorphisms (Wald $\chi^2=2.92$, df=1, p=0.087) on the TMTB. Elderly persons without an ApoE $\epsilon 4$ allele who reported a happy childhood had significantly better scores on the TMTB (OR=0.55; 95%CI=0.34-0.88; p=0.014) than $\epsilon 4$ allele carriers (OR=4.39; 95%CI=0.51-37.52; p=0.18). A sex interaction effect with loss of a parent during childhood was also found (Wald $\chi^2=5.23$, df=1, p=0.022); women, but not men having low scores on the Isaacs test if they had lost a parent during childhood (OR=1.95; 95%CI=1.25-3.06; p=0.003).

Changes in cognitive scores were examined over time in order to observe the relationship between childhood abuse and rate of cognitive decline. Performance at baseline was subtracted from that of either follow-up visit two or four years later. Most of the negative effects observed in cross-sectional analyses were also found longitudinally, notably the association between sharing of adult problems with children and decline on the Isaacs (OR=1.46; 95%CI=1.01-2.09; p=0.043) and Benton tests (OR=1.54; 95%CI= 1.09-2.17;

p=0.014) (data not shown). Some of the positive effects were also observed in the longitudinal analysis, notably having had a mother suffering from mental problems being associated with lower decline on the Benton (OR=0.69; 95%CI=0.46-1.02; p=0.065), and reporting a happy childhood (OR=0.56, 95%CI=0.35-0.89, p=0.014), and parents being perceived as having done their best (OR=0.63; 95%CI=0.37-1.08; p=0.090) being associated with lower decline on the TMTB. Severe abuse (sexual or physical abuse or excessive physical punishment) was also observed in association with decline on the Benton (OR=0.55; 95%CI=0.30-0.99, p=0.048), although numbers are small for sexual abuse. Some additional associations were found, such as a effect on the Dubois task for subjects with a father suffering from mental disorder (OR=0.55; 95%CI=0.32-0.96; p=0.034), a decline on the Isaacs test related to experience of verbal abuse (OR=1.75; 95%CI=1.02-2.99; p=0.041), and a decline on the TMTB associated with fathers having alcohol problems (OR=2.69; 95%CI=1.66-4.36; p<0.0001) and conflict at home (OR=1.47, 95%CI=1.03-2.09, p=0.033).

DISCUSSION

In this large population study of community-dwelling elderly we found 13% of this cohort reporting severe childhood abuse and neglect. Unlike studies of abused children we found no difference in IQ scores between severely abused and non-abused elderly. The removal of subjects from the study with a diagnosis of dementia may, however, have introduced a bias given that low IQ is a risk factor for dementia. After adjusting for multiple competing causes of poor cognitive functioning, childhood mistreatment appeared nonetheless to have some residual adverse effects on late-life cognitive performance, however this was related mostly to general long-term conditions of child-rearing (parents overly sharing their problems and being sent to a foster home or chronic difficulties with schoolmates) rather than to specific traumatic events. There were, however, very few reported cases of sexual and severe physical abuse in

our sample (n=26, 2.0%), precluding adequate exploration of these events which have been the central focus of studies with children. Under-reporting of sexual abuse in this elderly cohort is also likely.

Contrary to studies of children where childhood maltreatment has been associated with significant dysfunction in all areas of cognitive functioning, in this older population the effects appear to be less marked and limited to some traumatic events; excessive sharing of parental problems or, for women, early parental loss, being sent to a foster home or being mistreated by schoolmates. There are a number of possible reasons for this; the effects of abuse may decrease over time, abused children may have higher mortality, be more likely to be institutionalized, have recall bias or be more likely to not participate in adult studies of psychiatric disorder. As suggested above, the removal of subjects with dementia, who are more likely to have hippocampal damage and an ApoE4 allele may have significantly reduced the strength of associations between childhood events and cognitive disorder. Our analyses may also have over-adjusted and thus precluded the demonstration of an intermediary effect, with childhood abuse giving rise to greater vulnerability for other disorders such as cardio- and cerebro-vascular disease and depression, which in turn heighten risk for poor cognitive function in late-life. This would be coherent with recent studies based on longitudinal birth cohort data which suggest inflammation to be a developmental mediator linking childhood experience with pathologies such as depression, cardiac pathologies and neurological disorder (Danese *et al.*, 2008; Danese *et al.*, 2007).

On the other hand we found that positive childhood environment (having experienced a happy childhood, feeling that parents did their best, having had a normal education) to be strong promoting factors in relation to adult cognitive performance, notably on central executive functioning. While negative childhood factors and health has received a great deal of

attention, this is the first study to our knowledge to report the long-term impact of positive childhood environment, both on cognitive performance and decline across time. Elderly persons who have experienced a childhood characterized by parents appearing to do their best by the children, and who generally recall this as a happy period, have improved scores on tests of central executive functioning, verbal recall and retrieval even after adjustment for multiple health variables.

Interestingly we observed a lower risk of cognitive dysfunction associated with physical and sexual abuse, however, numbers in the latter group were too small (n=26) for us to be able to examine the impact of individual events..We also observed a reduction in risk for cognitive dysfunction in persons having a parent suffering from a mental disorder. These observations suggest a possible resilience effect, with adverse events leading in some persons to decreased vulnerability to cognitive impairment. Children neglected but without physical abuse have been shown in a previous study to have a greater capacity for problem solving, abstraction, and planning than non-abused children (Nolin and Ethier, 2007). In young foster children, the number of maltreatment types has been observed to be positively associated with capacity for everyday functioning (Pears and Fisher, 2005). On the other hand, adults who have suffered severe abuse with long term cognitive consequences may also refuse to take part in research studies. Our data also suggest above all that aggregate scores of traumatic events are less informative than estimates of individual traumatic events, since individual life events may have both a positive and a negative effect, which cancel each other out when using the sum score of events.

We only observed one gene-environment interaction effect for persons having reported a happy childhood who were more likely to have better performance in later life on the Trail test if they were not carriers of an ApoE ϵ 4 allele. It is difficult to interpret this result, and we

conclude only that ApoE ϵ 4 carriers are at increased risk for life-time lower cognitive performance, but that unlike non- ϵ 4 carriers, their performance is not improved by positive early environmental conditions.

Prospective follow-up of changes in cognitive performance over a four-year period suggested that experience of verbal abuse was associated with greater decline in verbal retrieval skills, and that having had a father with alcohol problems or experiencing conflict at home was associated with increased decline in executive functioning. These data also confirmed some associations already observed on cognitive impairment at base-line, notably sharing of parental problems with children having a significant negative effect on verbal retrieval. We also observed that a positive early environment characterized by a happy childhood is associated with lower decline in executive functioning. On the other hand having a father or mother suffering from a mental disorder is also associated with better performance on both visual and verbal memory over the follow-up period. The association of some environmental factors not only with lower cognitive performance, but also with increased decline over time, argues in favour of a persistent underlying biological vulnerability as has been suggested in previous neurophysiological studies of abused children.

The results of the present study support and extend observations in children with severe trauma suggesting a link between severe stress and alterations in brain structures and brain functions (Teicher *et al.* 2003; Nolin and Ethier, 2007). The fact that these alterations persist in the elderly also supports the hypothesis that early severe stress and maltreatment initiates a cascade of neurobiological events that have the potential for producing enduring changes in brain development, which may occur on multiple levels, from neurohumoral (especially the hypothalamic-pituitary-adrenal axis) to structural and functional.

CONCLUSION

Our general conclusion is that only some aspects of childhood adversity continue to have a negative effect on later-life cognitive functioning. They are moreover associated with general environmental conditions (fostering and over-sharing of parental problems, problems with schoolmates, loss of a parent for women and paternal alcohol problems) rather than with traumatic events such as physical and sexual abuse, humiliation and neglect, although verbal abuse is observed to be associated with increased rates of decline on a verbal retrieval task. The impact is less than that observed in children and younger adults, possibly due to a weakening of the effect of trauma over time, neuronal compensatory processes, or mortality effects. Our results may, however, have under-estimated the true association due to sampling (elderly persons who have experienced abuse may be under-represented) or recall bias (under-reporting of severe abuse), the exclusion of persons with dementia who have both hippocampal damage and a higher likelihood of an ApoE ϵ 4 allele.

While this large population study was able to control for many competing causes of cognitive dysfunction, notably illness, there may have been over-adjustment, thus precluding the examination of intermediary pathologies, notably depression, cardiac disorders and neuropathologies which may constitute a link between childhood environment and late-life cognitive functioning. Of particular interest are the apparent cognition-promoting effects of a positive early environment, which appear to persist into old age. Future studies are needed with more in-depth clinical examination of childhood experiences both to validate true cases of abuse and to ensure that control groups used in the analyses are not contaminated by false-negative reports. Such studies should also take into account the possible intermediary role of chronic illness.

Key Points

- In our community-dwelling sample 91 % of elderly people reported having experienced at least one adverse childhood event, of which 14.7 % reported severe physical, mental or sexual abuse.
- Childhood adversity does not appear to be associated with a general lowering of cognitive functioning, but rather poorer performance in specific areas.
- While moderate childhood adversity is observed to continue to have a negative effect on cognitive performance in later-life ,some more severe events appear to have the opposite effect suggestive of a resilience mechanism possibly linked to improved problem-solving capacity. Positive early environment continues to have cognition-promoting effects even in old age.
- Estimates of individual traumatic events will be more informative than aggregate scores of traumatic events, since individual life events may have both a positive and a negative effect, which cancel each other out when using the sum score of events.

CONFLICT OF INTEREST

All authors report no competing interests.

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Table 1. Relationship between sociodemographic, and clinical characteristics and cognitive tests.

| | <i>ISAACS</i> | | | <i>Benton</i> | | | <i>Dubois</i> | | | <i>TMTB</i> | | |
|-----------------------------------|---------------|--------------|----------------|---------------|---------------|----------------|---------------|--------------|----------------|-----------------|--------------|----------------|
| | <i>>42</i> | <i>≤42</i> | <i>P-value</i> | <i>≥11</i> | <i><11</i> | <i>P-value</i> | <i>>8</i> | <i>≤8</i> | <i>P-value</i> | <i>< 110</i> | <i>≥110</i> | <i>P-value</i> |
| | <i>N=954</i> | <i>N=328</i> | | <i>N=1057</i> | <i>N=225</i> | | <i>N=942</i> | <i>N=340</i> | | <i>N=958</i> | <i>N=324</i> | |
| | % | % | % | % | % | % | % | % | % | % | % | |
| Gender, women | 60.59 | 51.22 | 0.003 | 57.99 | 59.11 | 0.76 | 61.78 | 48.24 | <0.0001 | 55.95 | 64.81 | 0.005 |
| Age Group (years) | | | | | | | | | | | | |
| <70 | 40.78 | 33.54 | 0.005 | 40.11 | 33.33 | 0.07 | 41.30 | 32.35 | 0.001 | 41.86 | 30.25 | <0.0001 |
| [70-75[| 33.54 | 31.10 | | 33.21 | 31.56 | | 32.48 | 34.12 | | 34.13 | 29.32 | |
| [75-80[| 18.13 | 23.17 | | 18.54 | 23.56 | | 19.11 | 20.29 | | 17.85 | 24.07 | |
| ≥ 80 | 7.55 | 12.20 | | 8.14 | 11.56 | | 7.11 | 13.24 | | 6.16 | 16.36 | |
| Marital Status, widowed | 19.29 | 20.43 | 0.65 | 18.64 | 24.00 | 0.07 | 18.90 | 21.47 | 0.31 | 17.12 | 26.85 | 0.0001 |
| Education | | | | | | | | | | | | |
| High | 29.87 | 16.77 | <0.0001 | 28.19 | 18.67 | <0.0001 | 27.81 | 22.94 | 0.001 | 30.58 | 14.51 | <0.0001 |
| Medium-High | 26.73 | 16.16 | | 25.64 | 16.44 | | 24.42 | 22.94 | | 24.74 | 21.91 | |
| Medium-Low | 29.04 | 35.06 | | 30.18 | 32.44 | | 31.53 | 27.94 | | 30.90 | 29.63 | |
| Low | 14.36 | 32.01 | | 15.99 | 32.44 | | 16.24 | 26.18 | | 13.78 | 33.95 | |
| Chronic diseases | | | | | | | | | | | | |
| 0 | 29.45 | 25.30 | 0.029 | 28.86 | 26.22 | 0.60 | 29.83 | 24.41 | 0.012 | 30.06 | 23.46 | 0.021 |
| 1 | 40.04 | 36.28 | | 39.17 | 38.67 | | 39.92 | 36.76 | | 39.25 | 38.58 | |
| ≥ 2 | 30.50 | 38.41 | | 31.98 | 35.11 | | 30.25 | 38.82 | | 30.69 | 37.96 | |
| Recent life events | | | | | | | | | | | | |
| 0 | 42.77 | 39.94 | 0.30 | 42.10 | 41.78 | 0.77 | 42.14 | 41.76 | 0.70 | 42.28 | 41.36 | 0.15 |
| 1 | 35.43 | 34.15 | | 34.72 | 36.89 | | 35.56 | 33.82 | | 36.12 | 32.10 | |
| ≥2 | 21.80 | 25.91 | | 23.18 | 21.33 | | 22.29 | 24.41 | | 21.61 | 26.54 | |
| APOE ε4 | 19.81 | 16.46 | 0.18 | 19.30 | 17.33 | 0.49 | 19.43 | 17.65 | 0.47 | 20.35 | 14.81 | 0.030 |
| CESDT≥16 or antidepressant intake | 26.10 | 31.10 | 0.08 | 26.02 | 33.78 | 0.02 | 27.81 | 26.18 | 0.56 | 25.47 | 33.02 | 0.008 |
| NART Score ≤18 | 20.75 | 42.38 | <0.0001 | 22.61 | 43.56 | <0.0001 | 23.14 | 35.00 | <0.0001 | 19.83 | 45.37 | <0.0001 |

Table 2 Significant associations (odds ratios, confidence intervals and significance levels) between specific childhood events and performance on cognitive tests adjusted by potential confounders

A – Effects on verbal fluency and on visual memory

| | Isaacs ¹ | | Benton ² | | | | | |
|---|---------------------|---------------|---------------------|---------|----------------|--------------|------------------|---------|
| | > 42 N=954 | ≤ 42 N=328 | | | ≥ 11 N=1057 | <11 N=225 | | |
| | % | % | OR [95 %CI] | p-value | % | % | OR [95 %CI] | p-value |
| <i>Parents too often shared their problems with children</i> | 12.58 | 20.43 | 1.68 [1.18-2.38] | 0.004 | | | | |
| <i>Death of a parent</i> | 14.78 | 21.95 | 1.43 [1.03-2.00] | 0.035 | | | | |
| <i>Sent to a foster family</i> | | | | | 1.70 | 4.00 | 2.23 [0.96-5.15] | 0.062 |
| <i>Mistreatment at school by schoolmates</i> | | | | | 1.70 | 4.00 | 2.27 [0.98-5.29] | 0.057 |
| <i>Normal education</i> | | | | | 95.08 | 91.11 | 0.60 [0.34-1.05] | 0.072 |
| <i>Physical and/or sexual abuse and/or excessive physical punishment for misbehaviour</i> | 6.71 | 4.27 | 0.55 [0.30-1.02] | 0.057 | | | | |
| <i>Humiliation, harassment or mental cruelty</i> | 3.98 | 1.83 | 0.39 [0.16-0.95] | 0.038 | | | | |
| <i>Mother suffered from mental problems</i> | | | | | 13.06 | 8.44 | 0.60 [0.36-1.01] | 0.056 |

¹ Adjusted by gender, age, education, CESDT≥16 or antidepressant intake and chronic diseases

² Adjusted by gender, age, education, CESDT≥16 or antidepressant intake and widowed

B – Effects on verbal memory and on executive function

| | Dubois ¹ | | TMTB ² | | | | | |
|---|---------------------|--------------|-------------------|---------|---------------|----------------|------------------|---------|
| | >8 N=942 | ≤ 8 N=340 | | | <110 N=958 | ≥ 110 N=324 | | |
| | % | % | OR [95 % CI] | p-value | % | % | OR [95 % CI] | p-value |
| <i>Impression that parents did their best</i> | 94.80 | 92.06 | 0.63 [0.38-1.04] | 0.074 | 94.89 | 91.67 | 0.61 [0.36-1.02] | 0.062 |
| <i>Happy childhood</i> | | | | | 92.90 | 88.27 | 0.64 [0.41-1.00] | 0.051 |
| <i>Normal education</i> | | | | | 95.51 | 91.05 | 0.56 [0.33-0.94] | 0.029 |
| <i>Mother suffered from mental problems</i> | 13.80 | 7.94 | 0.61 [0.39-0.95] | 0.035 | | | | |

¹ Adjusted by gender, age, education and chronic diseases

² Adjusted by gender, age, education, CESDT≥16 or antidepressant intake, chronic diseases and ApoE ε4